Synthetic investigations of isoquinoline alkaloids.

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Synthetic Investigations of Isoquinoline Alkaloids

Submitted by E.P. Tiley
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of the University of Bath
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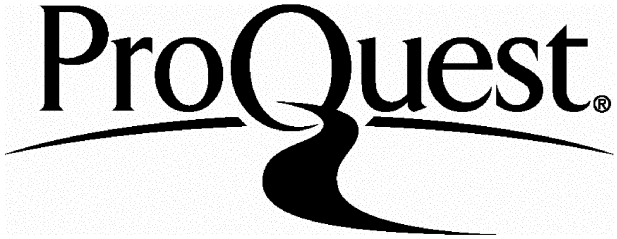


The author would like to thank the Science Research Council and Glaxo Ltd. for an Industrial Studentship, and to thank Dr. S.F. Dyke for his interest and supervision of these investigations towards alkaloid syntheses.

Contents

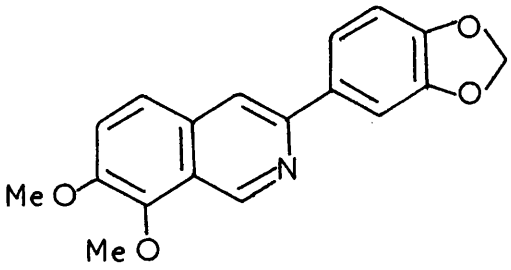
SUMMARY

Several synthetic routes towards 3-aryl-7,8-dimethoxyisoquinolines were investigated to provide intermediates for berbines and benzo-[c]-phenanthridines. A facile synthesis of 3-aryl-7,8-dioxygenated isocoumarins was obtained by conversions to isoquinoline derivatives were unsuccessful. A novel route to an α-benzylaminophenyl-acetaldehyde dimethyl acetal was accomplished, with subsequent ring closure to a 3-aryl-7,8-dimethoxyisoquinoline.

The preparation of dissymmetrically substituted desoxy-benzoins was briefly investigated and, through the intermediate conversion of a desoxybenzoin to a 3-aryl-8-hydroxy-7-methoxy-isoquinoline, the alkaloid Berberastine was synthesized.

INTRODUCTION

A major problem in the synthesis of isoquinolines, particularly isoquinoline alkaloids, is the preparation of 7,8-dioxygenated derivatives. These investigations were concerned with the syntheses of 3-(3,4-methylenedioxyphenyl)-7,8-dimethoxyisoquinolines (1) and the application of such compounds as intermediates towards the syntheses of natural products.



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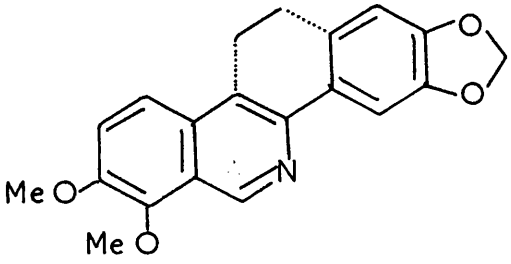

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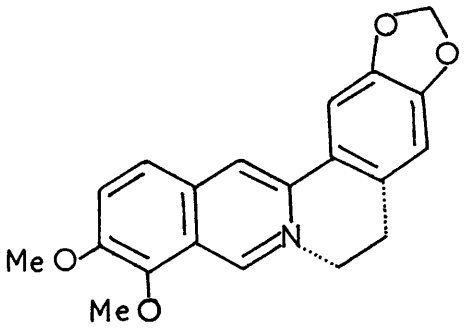

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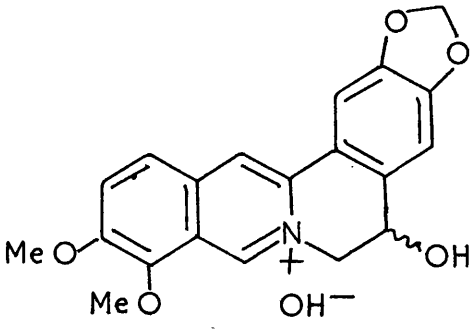

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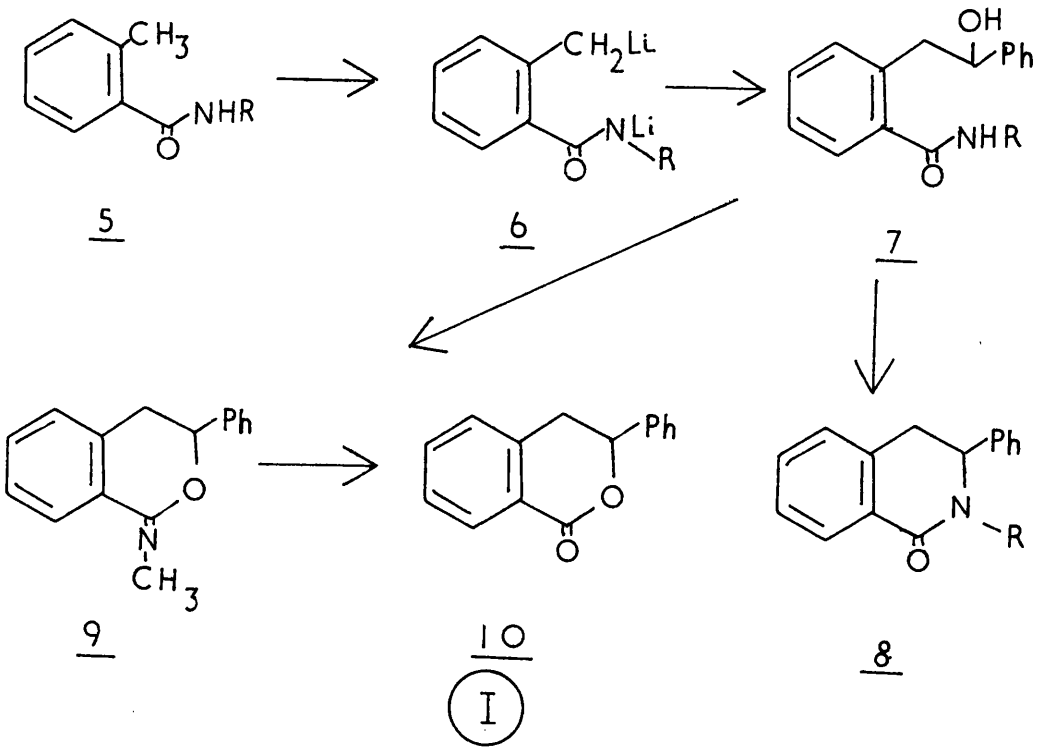
By the addition of a two-carbon bridge from C-4 to the 3-aryl group (2), the derivation of benzo-[c]-phenanthridines[1,2,3,4] is evident. Similarly, by the addition

of a two-carbon bridge from nitrogen to the 3-aryl group (3), the berbine skeleton may be obtained.

The principle target of synthesis was the alkaloid Berberastine[5] (4), one of only three known berbines[5a] with an hydroxyl group at C-5.

3-Arylisoquinolines

Various new syntheses of 3-arylisoquinolines have been reported since this topic was earlier reviewed[6] by the author. From investigations[7,8] by Hauser *et al* into *ortho*-lithiation of aromatic carboxamides, it appeared that a useful synthetic route to 3-aryl-3,4-dihydroisocarbostyrils had been developed (Scheme I). Lithiation of a 2-methylbenzamide (5; R=Ph), and reaction of the 2-lithiomethyl derivative (6; R=Ph) with benzaldehyde gave[7] an hydroxy-amide (7; R=Ph). Acid promoted cyclization was reported to afford a 3-aryl-3,4-dihydro-isocarbostyril (8; R=Ph). Doubt regarding the generality of this cyclization, and possibly the identity of (8; R=Ph), was raised by the observations reported by Bailey and DeGrazia.[9,10] Using a similar hydroxy-amide (7; R=CH_3), acid promoted cyclization afforded the 1-methyliminoisochroman (9) which was readily hydrolysed to the 3,4-dihydroisocoumarin (10). Presumably the course of cyclization depends on the relative nucleophilicities of the nitrogen and oxygen functions in the amide group, and the cyclization by oxygen to (9) compares with the preferential, but not exclusive,[11,12] O-alkylation of amides.



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(I)

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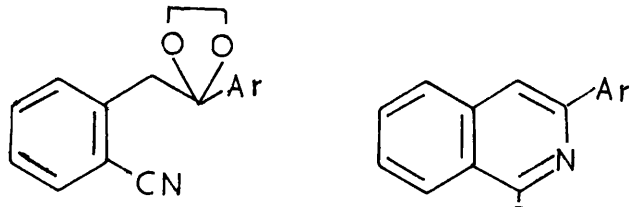

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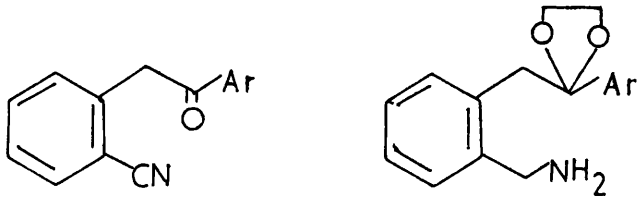

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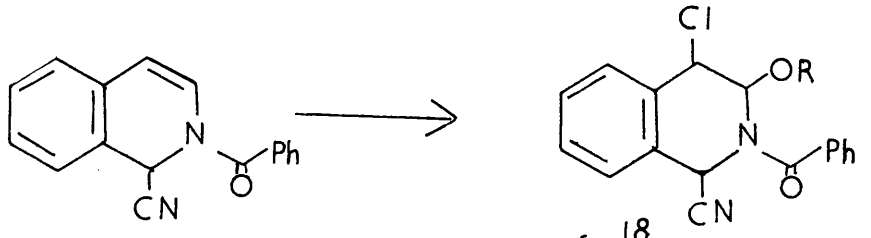
Adaptations of the Hauser ortho-lithiation have been reported. Treatment of 2-methylbenzonitrile (11) with base[13] and a methylbenzoate gave a desoxybenzoin (13; Ar=phenyl or 4-methoxyphenyl). Protection of the ketone as a ketal (15), reduction of the nitrile to an amine (16) and subsequent cyclization and oxidation then afforded a 3-arylisoquinoline (14; R=H, Ar=phenyl or 4-methoxyphenyl). Reaction of (11) with base and an aromatic nitrile was reported[14] to give a 3-arylisoquinoline ($R=NH_2$) directly.

Reissert compounds[15,16] such as (17) can readily be obtained from aromatic isoquinolines and an interesting rearrangement of (17) to 3-arylisoquinolines (19; R=H or CHO) has been demonstrated[17] by Kirby et al. Compound (17) was oxidized to (18) by hypochlorites and this intermediate was rearranged by aqueous or alcoholic bases to (20) or (19) respectively, whereas reaction with triethylamine afforded (21). It would appear that the general usefulness of this type of reaction sequence would depend on the susceptibility of alkoxyl-substituted aryl groups to oxidation by reagents necessary to produce (18) (Scheme II).

The efficiency of cyclization of methyl ($\pm$) 3-amino-2,3-diarylpropionates to tetrahydroisoquinolines by the Pictet-Spengler method has been reported[18,19] to show a marked dependence on initial stereochemistry. The erythro compounds (22; Ar=phenyl or 3,4-methylenedioxyphenyl) readily afforded the trans isoquinolines (23) whereas the threo compounds (24) gave the corresponding cis isoquinolines



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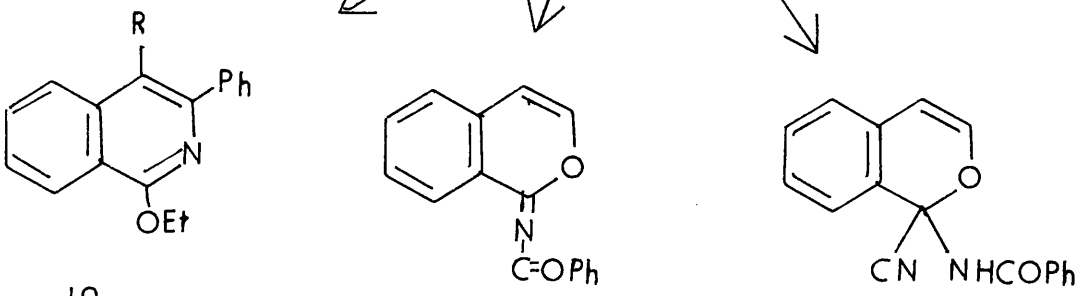

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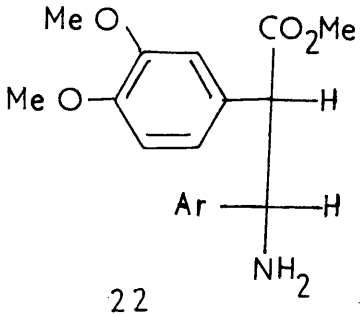
(II)



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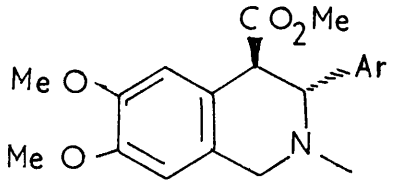

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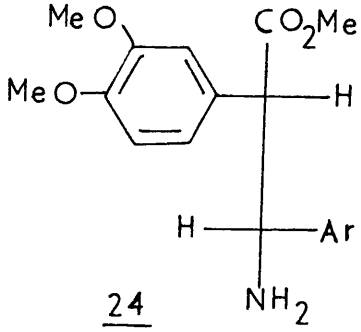

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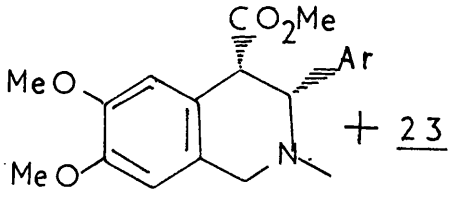

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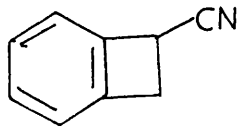
(25) in only poor yields, along with some trans isoquinolines (23). Facile production of the cis compounds (25) was presumably prevented by the need to adopt the eclipsed conformation prior to cyclization. Despite such problems, the ease of access to 4-carbomethoxy-3-arylisoquinolines is of considerable interest as a potential route to benzo-[c]-phenanthridines. An oxygen analogue of a benzo-[c]-phenanthridine has been obtained[20] from a related isocoumarin by conversion of a 4-carboxyl group to a 4-chloroacetyl group and subsequent ring closure. Though annelation of such a 4-carboxyisoquinoline to an 11-oxygenated benzo- c - phenanthridine seems feasible, further modification to produce a 7,8-dioxygenated precursor, rather than the reported 6,7-dioxygenated compounds (23) and (25), would be desirable.

Thermolysis of benzocyclobutanes gives rise to the highly reactive o-quinone dimethide species which may be trapped by a variety[21,22,23] of reagents (vide infra). Intramolecular trapping (28) to form a 3-arylisochromen (29) has been accomplished[24] by thermolysis of a 3-benzoylbenzo- 1,2 - cyclobutane (27). A reactive species similar to (28) was produced[25] by base promoted elimination of hydrogen chloride from 2-cyanomethylbenzoyl chloride (30) to afford (31), which dimerized to 3-(2-cyanomethylphenyl)-4-cyanoisocoumarin (32).

Thermolytic ring closure of α-phenylstyrylisocyanate (33; R=H) has been reported[26] to give 3-phenylisocarbostyryl (34; R=H). In view of the success of similar annelations to ring systems bearing electron-withdrawing substituents[27] this type of ring closure could be of interest when applied to styryl



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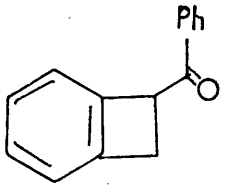

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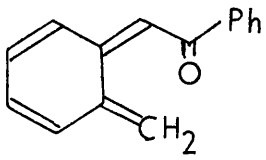

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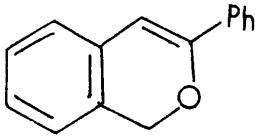

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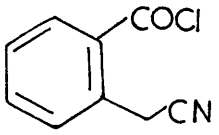

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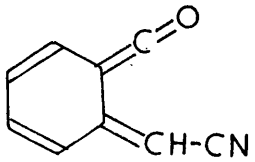

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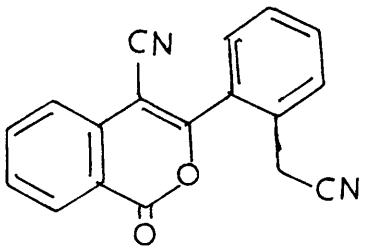

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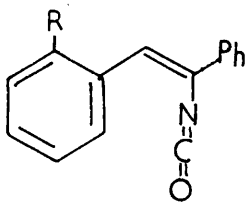

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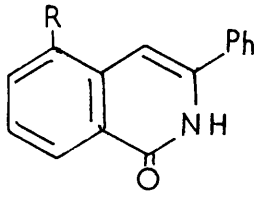

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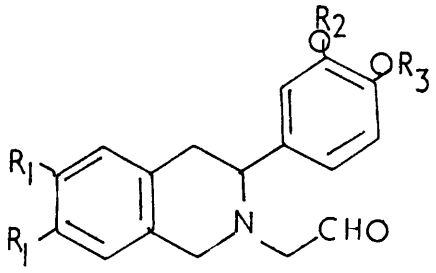

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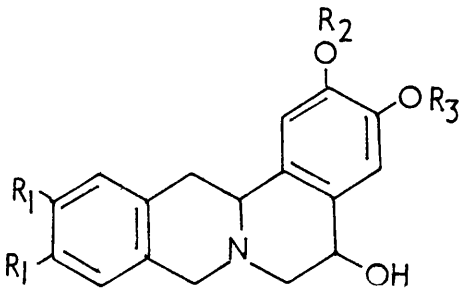

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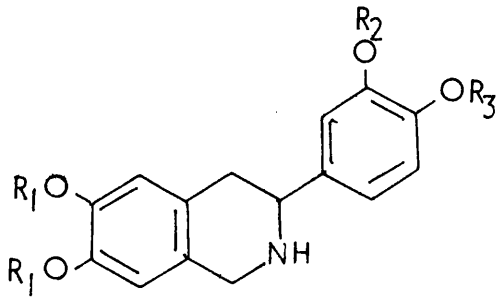

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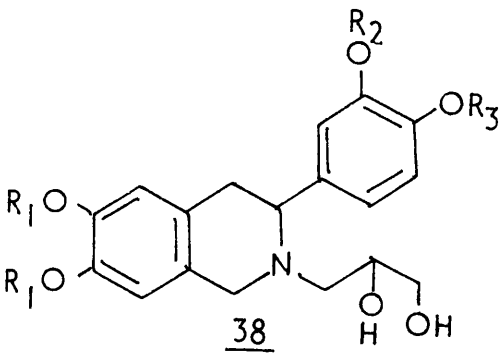

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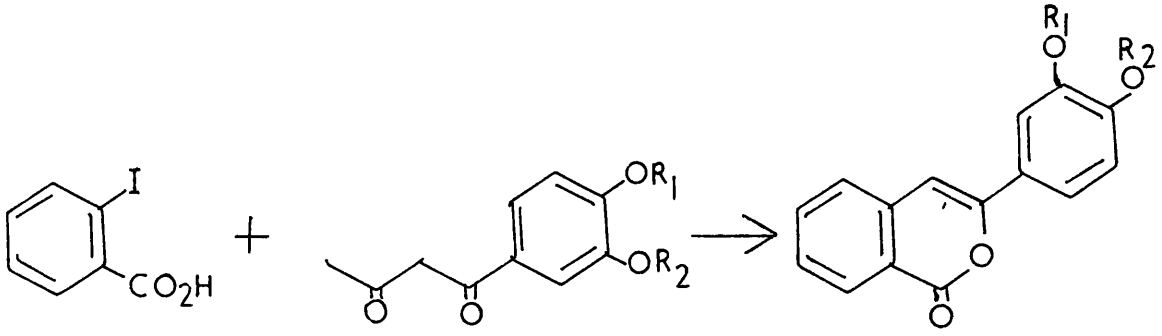
systems bearing an ortho blocking group such as (33; R=Br etc.). Isocyanates of type (33) are readily obtained by condensation of a benzaldehyde with a phenylacetic acid to afford[28] an α-arylcinnamic acid, and subsequent synthesis of the isocyanate group through an acyl azide.

5-Hydroxyberbines

The only previous syntheses of 5-hydroxyberbines (36) have been by Dyke, Hardy, et al, by the cyclization[29,30,31] of 3-aryl-1,2,3,4-tetrahydroisoquinol-2-yl acetaldehydes (35; R_1=H or CH_3O, R_2=R_3=CH_3 or R_2+ R_3=CH_2). Two methods were used to obtain the key compound (35). Reaction of, for example, 6,7,3',4'-tetramethoxy-1,2,3,4-tetrahydro-isoquinoline[6,32,33] (37; R_1=R_2=R_3=CH_3) with glycidol afforded[29,30] the diol (38), cleavage of which with sodium periodate gave the aldehyde (35; R_1=OCH_3, R_2=R_3=CH_3). Alternatively, arylation of the -diketone (40; R_1=R_2=CH_3 or R_1+ R_2=CH_2) with 2-iodobenzoic acid afforded[30,31,33] the isocoumarin (41) which readily condensed with aminacetal to give the isocarbostyril (42), reduction of which then gave the necessary N-acetaldehyde dimethyl acetal (43). Although dehydrogenation of simple 4-hydroxy-1,2,3,4-tetrahydro-isoquinolines gives fully aromatic isoquinolines, dehydrogenation of compounds of type (36) with ethanolic iodine buffered with sodium acetate afforded only the berberastine analogues of type (44) and not the hexadehydro-berbines of type (45). Acid promoted cyclization of the iso-carbostyril-acetal (42) gave only the cyclized and dehydrated



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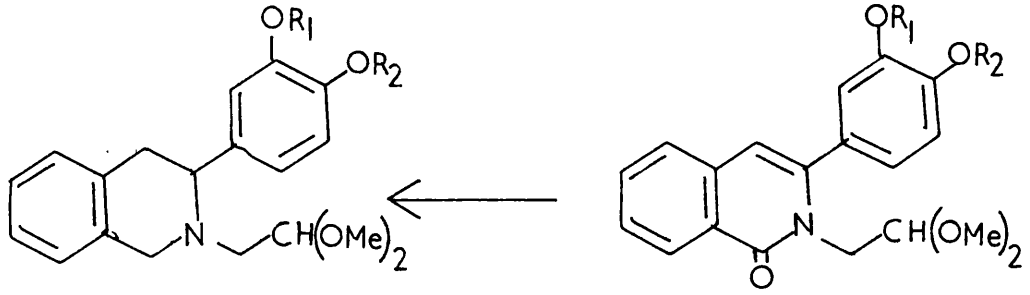

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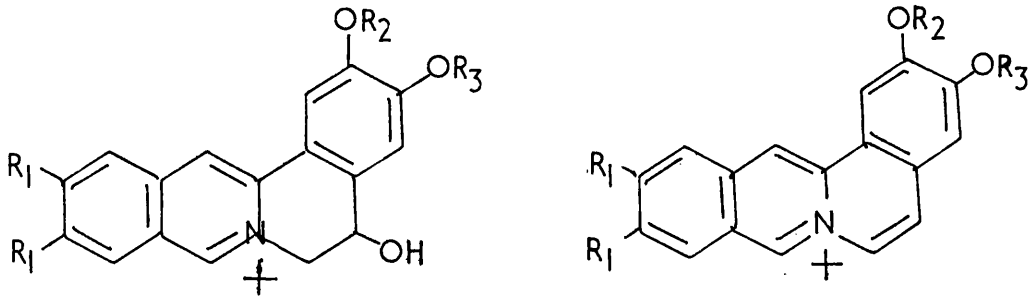

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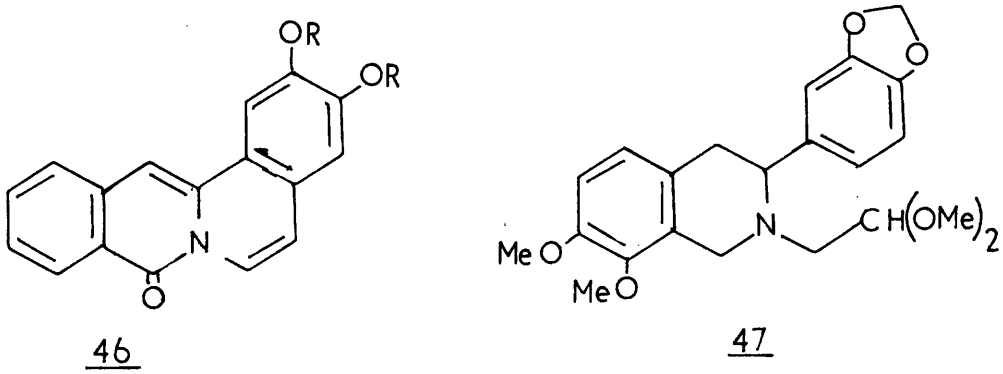

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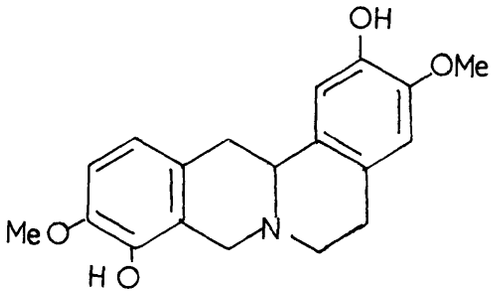
III

product, (46).

It was thus evident that a synthesis of Berberastine might be accomplished by such a method, provided that a route to the 7,8-dimethoxy analogue, eg. (47), of (35), or (43), could be achieved.

Berbines

Ring closure of 1-benzylisoquinolines under "physiological conditions" has been the subject of various investigations[34,35,36,37,38,39,40] with most useful results. For example, reaction of norreticuline and formaldehyde at pH 6.3 gave[36] a mixture of scoulerine (48) and coreximine (49) in a 2:1 ratio, whereas a similar reaction, conducted[37] at unspecified pH, gave mostly coreximine (49). ("Old" formalin solutions have been found to be quite acidic so the synthesis of coreximine by Kametani *et al*, since the pH was unspecified, could have resulted from using such "old" formalin). Such control of reaction course by pH was also observed[38] in the cyclization of (50) to the kikemanine precursor (51). At pH 6.4, *ortho*- and *para*-closure occured to afford a separable mixture of (51) and (52), but if the hydrochloride salt of (50) was used, presumably resulting in a more acidic reaction media, then only *para*-closure (52) was observed. The synthesis of kikemanine (53) was accomplished from (51) by methylation to (54; R=$PhCH_2$), followed by cleavage of the benzyl ether to afford (54; R=OH). The synthesis of capaurimine[41] (55) was accomplished[39] in a similar manner. This technique provides a most useful synthetic



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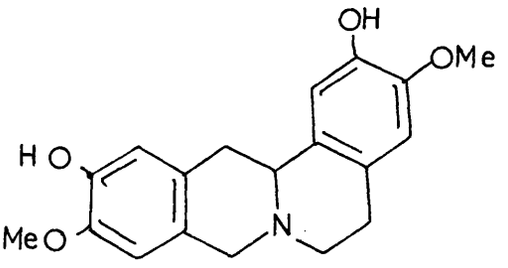

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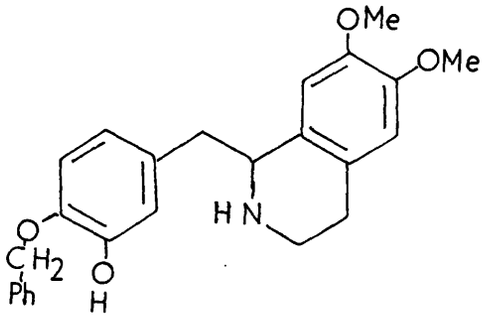

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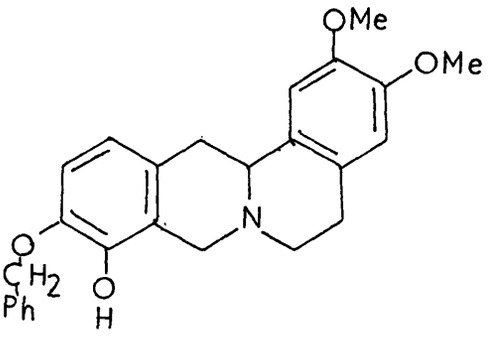

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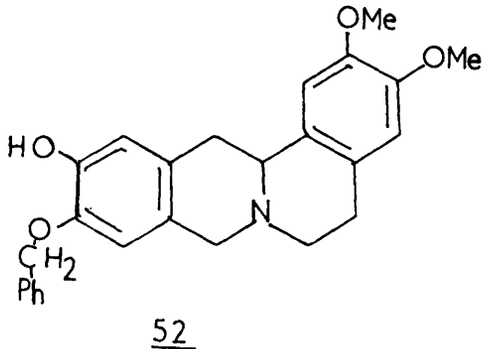

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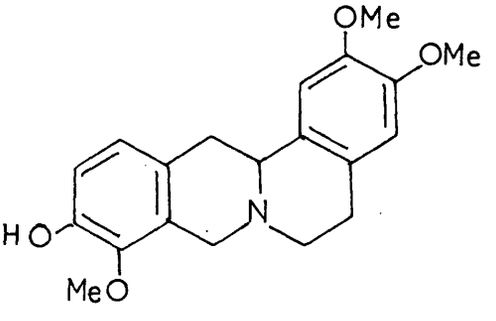

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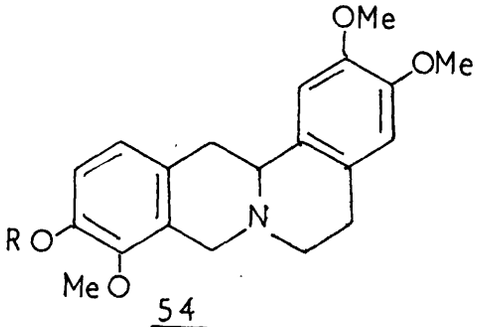

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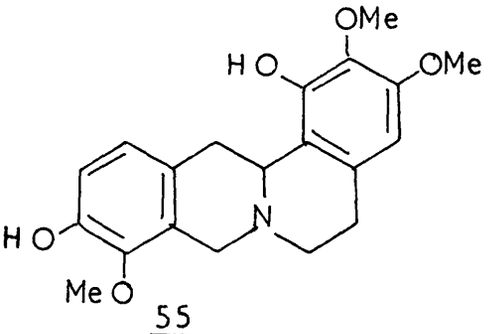


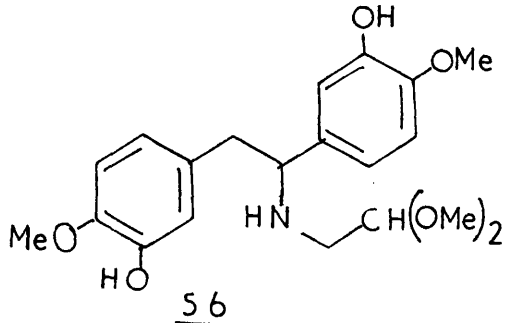
55

route to 9-methoxy-10-hydroxyberbines.

An extrapolation of pH-controlled ring closures to the synthesis of 3-arylisoquinolines, and subsequently of berbines, has been by Battersby,[42] illustrated by the sequence (56) to (58). Cyclization of the 1,2-diaryl-ethylamine (56) with aqueous ethanolic formaldehyde gave a mixture of isoquinolines (57; R_1=H, R_2=OH) and (57; R_1=OH, R_2=H). The components were not separated by cyclized to a mixture of 5-hydroxyberbines (58; R_1=H, R_2=R_3=OH) and (58; R_2=H, R_1=R_3=OH), and the hydroxyl group at C-5 was removed by hydrogenolysis to afford a separable mixture of (58; R_1=R_3=H, R_2=OH) and (58; R_2=R_3=H, R_1=OH). The removal of the alcoholic group was presumably facilitated by ready formation of the quinone methide (59).

Apart from the now established method of pH-controlled ring closures ortho to a phenolic group, one obvious way in which specific ortho ring closure might also be effected is by use of a blocking group at the para position. Early attempts at such ring closures met with failure[43,44,45] though. For example, Haworth and Perkin[43] attempted to obtain 12-bromocanadine (61) by the action of formaldehyde on the 1-benzylisoquinoline (60) but the product was found to be that derived from displacement of bromine, tetrahydro berberine (62).

That bromine may serve successfully as a blocking group was demonstrated[46] by Kametani et al with the synthesis of 5-bromo-7,8-dimethoxy-3,4-dihydroisocarbostyril (63) from N-carboethoxy-2-(3,4-dimethoxyphenyl) ethylamine (64).



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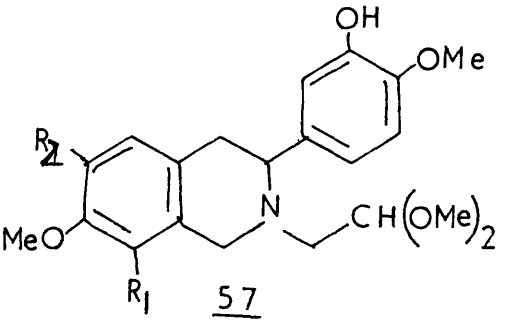

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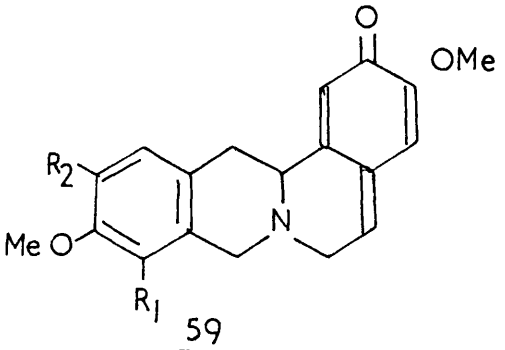

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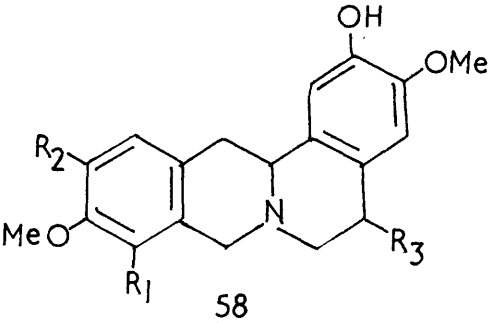

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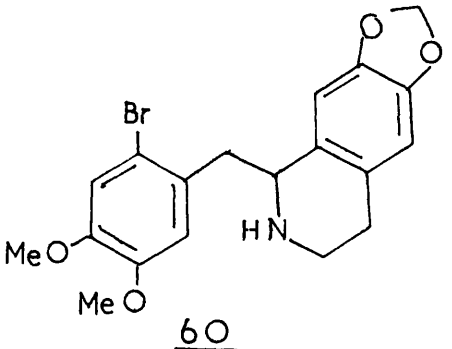

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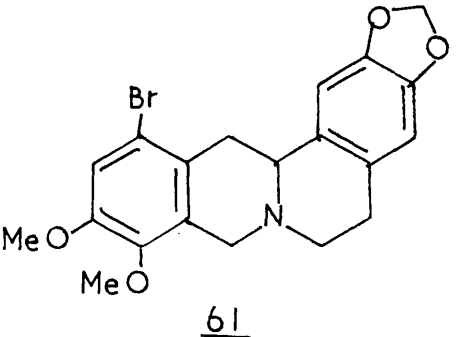

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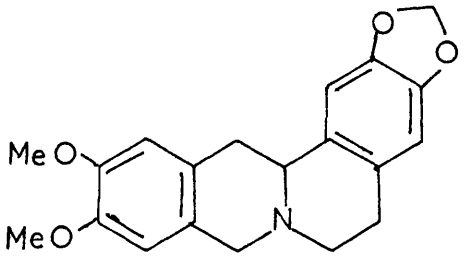

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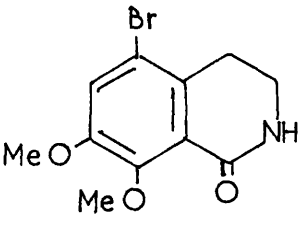

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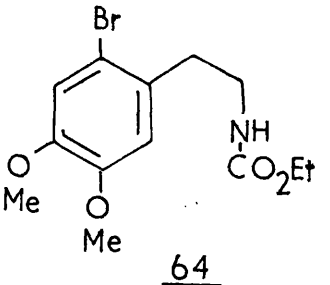

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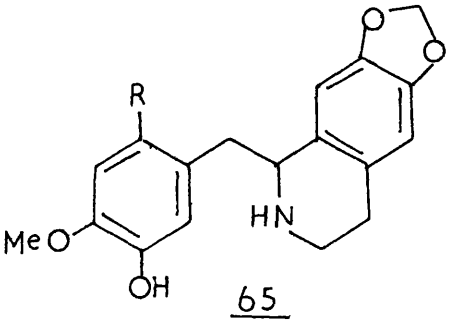

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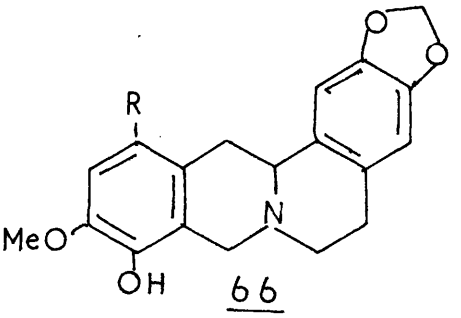
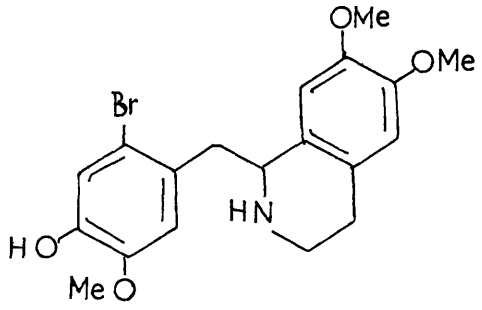


66

Use of phenolic compounds rather than methyl ethers, and using a bromine group to block the para-position, has enabled ring closures to berbines to be carried out with formaldehyde.[47,48] For example, nandanine (66; R=H) has been obtained from (65) by ring closure with formaldehyde to (66; R=Br) and subsequent hydrogenolysis of the bromine group. That a free phenolic group must be present ortho to the site of closure, in such reactions involving blocking groups, was illustrated by the failure[49] of the attempted cyclization of the 1-(2'-bromo-4'-hydroxy-5'-methoxybenzyl) isoquinoline (67) to the berbine (68) on treatment with formaldehyde.

The use of an amino group as an aid to difficultly accessible berbines has received some attention. A synthesis of O-methylcaseadine (69; R=H) was accomplished[50] by cyclization of the carbamate (70) to the mixture of 1-benzyl-isoquinolines (71; R_1=OCH_3, R_2=$NHCO_2Et$), and (71; R_1=$NHCO_2Et$, R_2=OCH_3). The desired berbine was obtained in the usual manner, and the product (69; R=NH_2) was deaminated to (69; R=H). The influence of an amino group on the direction of the Mannich reaction to berbines has also been reported by Ishiwata and Hakura,[51] and it was found that the 1-benzyl-isoquinoline (72; R_1=R_2=OCH_3 or R_1+ R_2= -OCH_2O-) gave a mixture of products derived from cyclization ortho (73; R_3=NH_2, R_4=OCH_3) and para (73; R_3=OCH_3, R_4=NH_2) to the amino group. Such compounds were susceptible to both deaminations and replacement of the amino group by hydroxyl.



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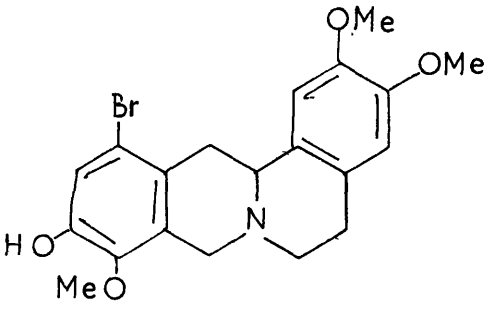

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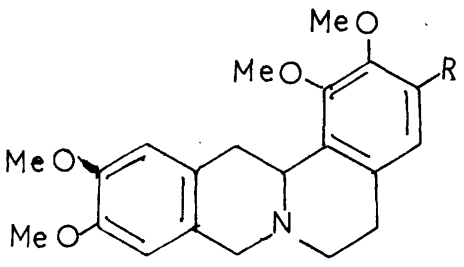

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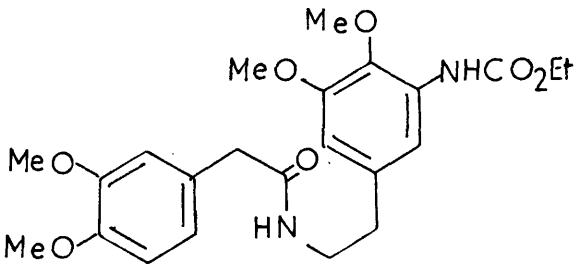

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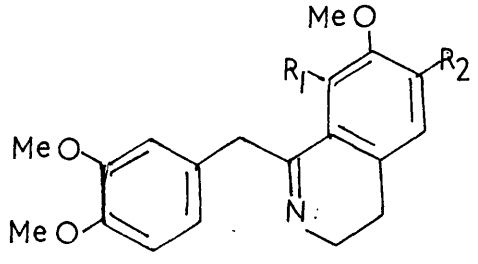

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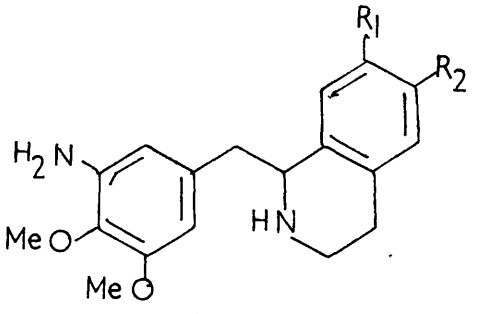

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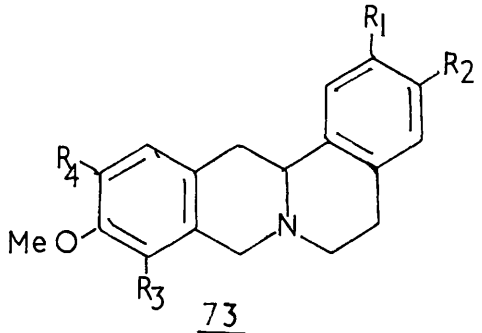

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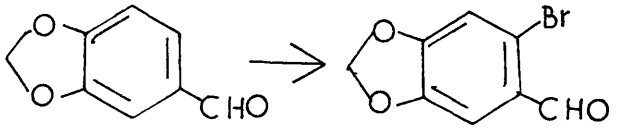

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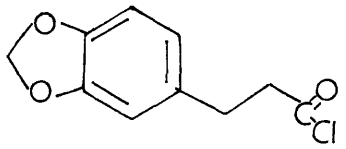

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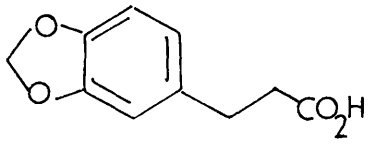

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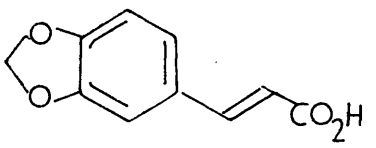
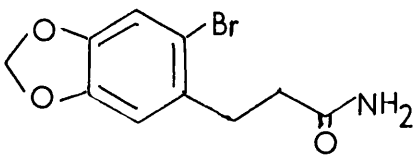


76

Benzo-[c]-phenanthridines

A major achievement in this class of alkaloids has been the total synthesis of dl-chelidenine by Oppolzer and Keller,[52] the route used being outlined overleaf. This is also the only preparation of an 11-oxygenated benzo- c -phenanthridine, although 11-carboxybenzo- c -phenanthridines are known.[53,54] The intermediates such as the benzocyclobutene urethane (98) and the 6-vinylbenzylbromide (95) are accessible by known methods[55,56,57] but their presumed synthetic routes are provided for convenience. The key step in this synthesis was the thermal rearrangement of the acetylenic benzocyclobutene (101) to the tetrahydrobenzo-[c]-phenanthridine (102). This reaction was an extrapolation of other investigations by Oppolzer towards intramolecular cyclizations of o-quinodimethanes.[21,22,23] Since the olefin is not significantly non-planar, the cis-addition of diborane can, and did, occur from both sides of the molecule resulting in a 1:1 mixture of the desired cis 4b-10b alcohol (103) and the undesired trans 4b-10b alcohol (104). Unfortunately production of the correct geometry of the ring junction necessarily resulted in the incorrect 'equatorial' stereochemistry of the alcohol. Jones oxidation of the alcohol (103) afforded the ketone (105) and reduction of the ketone with sodium borohydride occured from the least hindered side, stereospecifically. It remained only to deprotect the nitrogen group by hydrogenolysis of the benzyloxycarbonyl group to obtain dl-norchelidonine, (107) and to methylate to dl-chelidonine (108).



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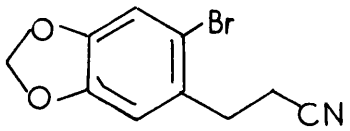

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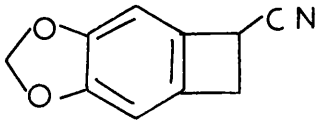

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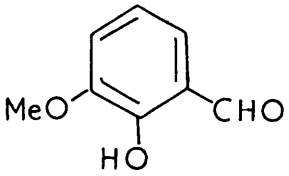

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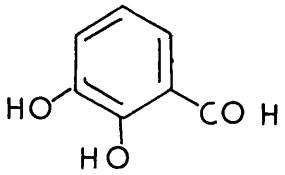

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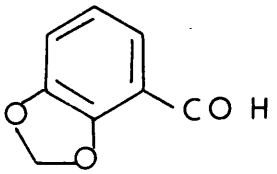

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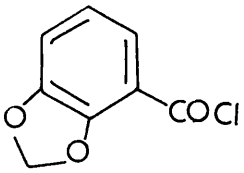

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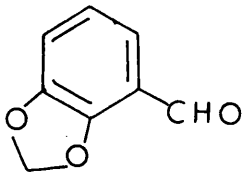

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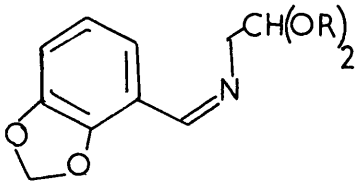

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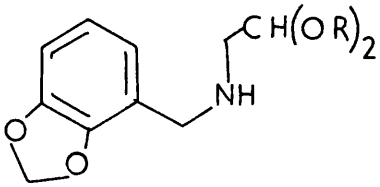

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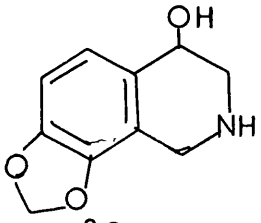

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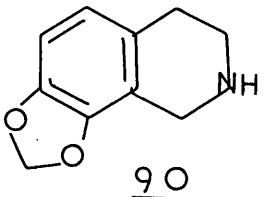

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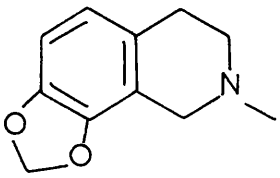

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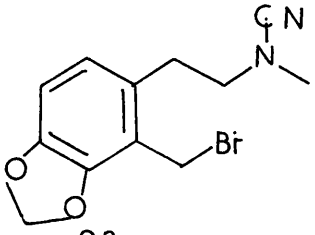

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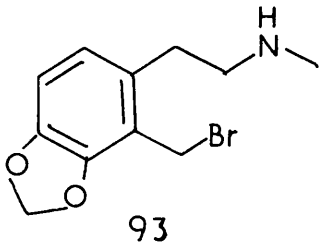

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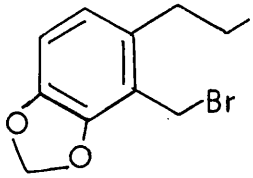

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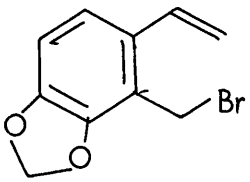

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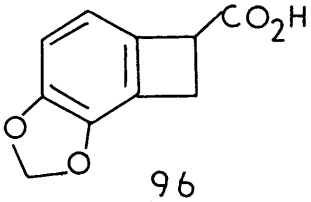

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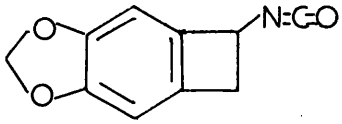

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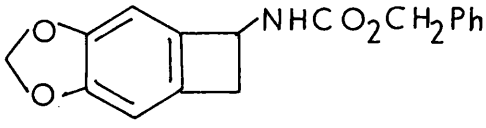

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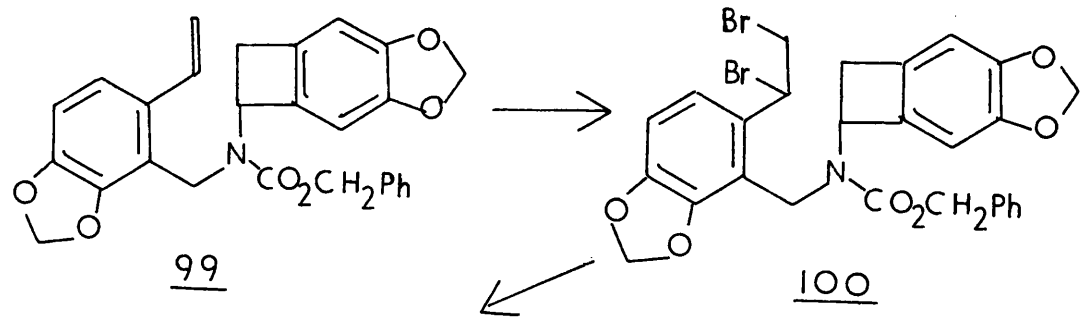

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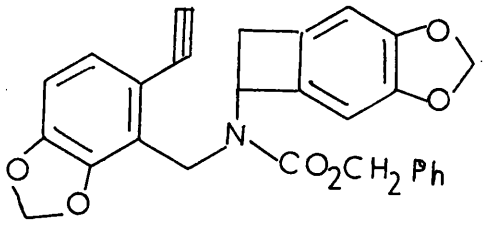

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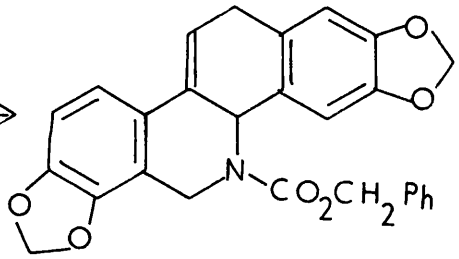

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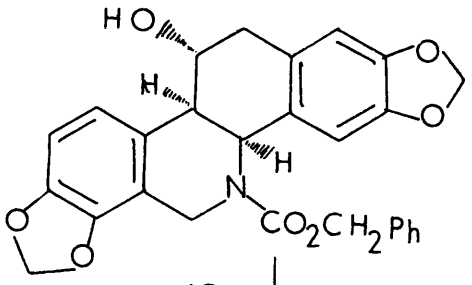

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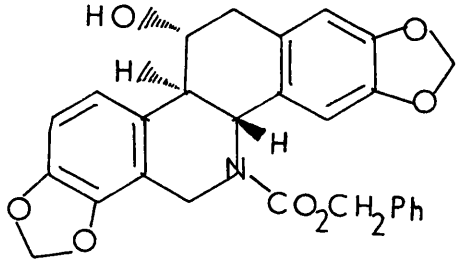

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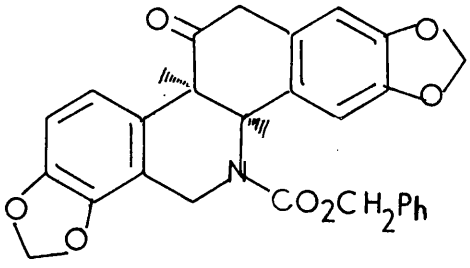

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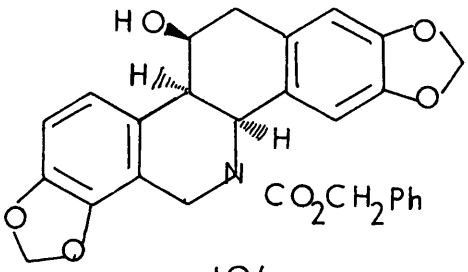

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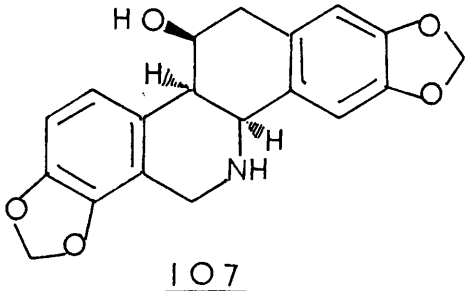

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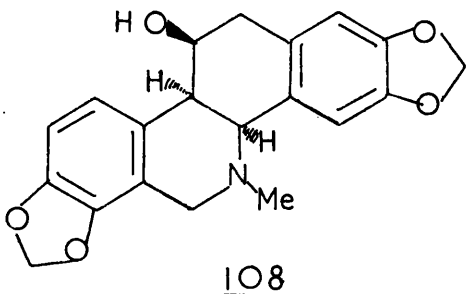
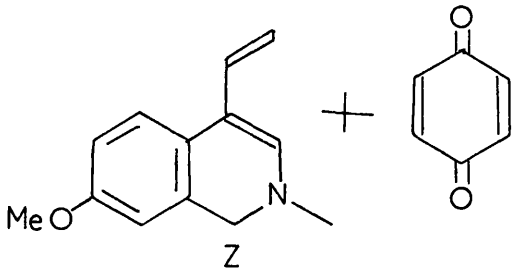


108

IV

Compounds resembling the olefin (102), such as (115), have been obtained[58] by Diels-Alder reactions with 2-methyl-4-vinyl-1,2-dihydroisoquinolines (109) and dienophiles such as 1,4-benzoquinone (110) but difficulties with very ready acid oxidation of such compounds were experienced and introduction of a C-11 hydroxyl group was unsuccessful. Dienes of type (109) were obtained by Vilsmeier formylation of 4-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (112), presumably though a 1,2-dihydroisoquinoline (113), to obtain a 4-formyl-1,2-dihydroisoquinoline (114; $Z=H_2$), the latter being readily oxidized to an isocarbostyril (114; Z=O). The formyl group is part of a vinologous amide and has no aldehydic character, whereas in the oxidized compound.(114; Z=O), the formyl group readily reacted with methylmagnesium iodide to afford the alcohol (115) which, when thermally dehydrated in the presence of a dienophile, afforded[58] phenandridones or benzo-[c]-phenanthridines.

Although there have been few significant investigations into the syntheses of benzo-[c]-phenanthridines since the subject was last reviewed by the author,[6] there have been some surprises regarding the structures of recently isolated benzo-[c]-phenanthridines. One structural claim that was biosynthetically disconcerting was that for bocconine[59] as (116), but Slavik and Santavy have shown[60] that bocconine chloride is identical to chelirubine chloride, and the biosynthetically reasonable structure (117) has been proposed[61] for chelirubine chloride.



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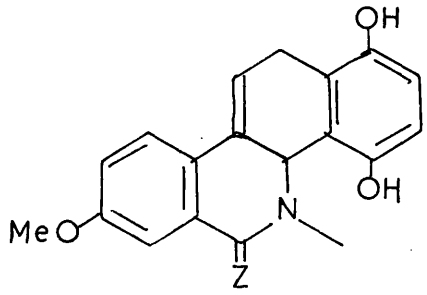

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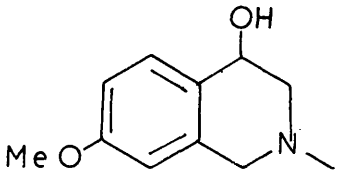

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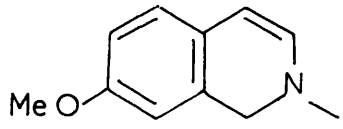

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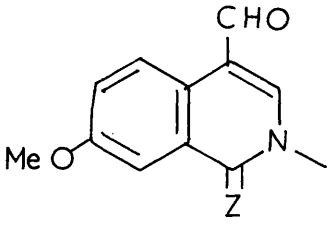

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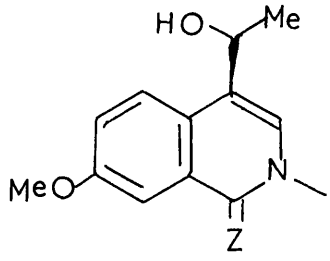

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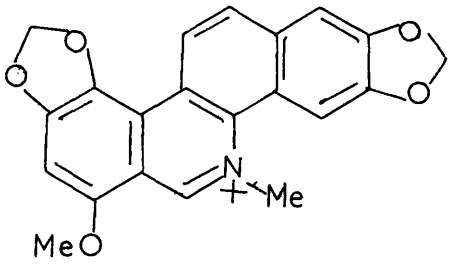
(V)



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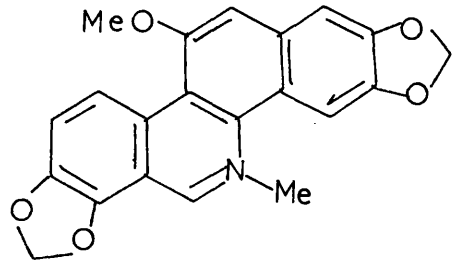

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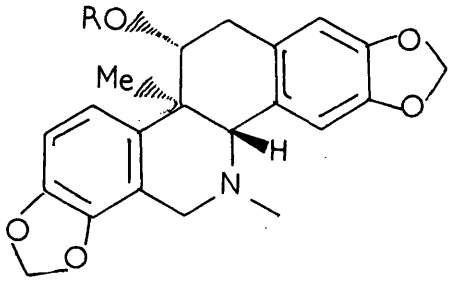

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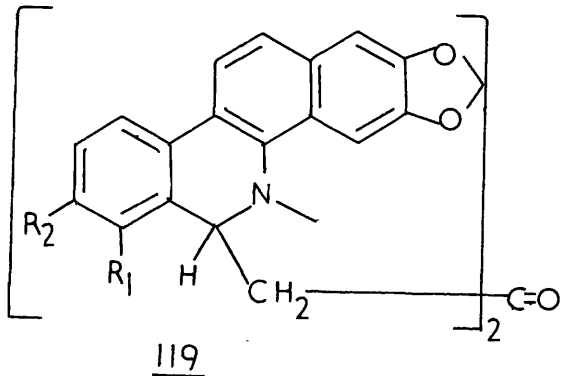
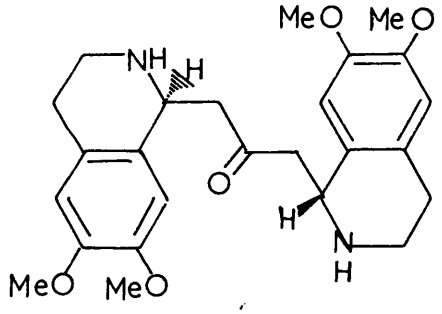


119

Two isomers of corynoline and acetylcorynoline have recently been isolated,[62] where the B/C ring junction has been found to be trans-fused. These compounds, isocorynoline (118; R=H) and acetylisocorynoline (118; R=OAc) are the only known examples of such trans-fused hexahydrobenzo-[c]-phenanthridines.

Two acetonyl dimers[63,64] of both chelerythrine (119; R_1=R_2 =OCH_3) and Sanguinarine (119; R_1 + R_2=OCH_2O), the latter named chelidimerine,[64,65] are known and both have been synthesized from the corresponding monomeric benzo-[c]-phenanthridines and acetonedicarboxylic acid. This method of linking two 3,4-dihydroisoquinolines through an acetonyl bridge is similar to that used in a synthesis of emetine.[66] The existence of chelidimerine in both meso and (+) forms also warrants comparison with the emetine precursor (120).

Further variations of the known photochemical conversion of anhydroprotopine (121) to sanguinarine (122) have been reported. From an attempted Oppenauer oxidation of (±) ophiocarpine (123) the 3-(6'-vinylaryl)-4-hydroxyisoquinoline (124; R=H) was obtained,[67] and the corresponding methyl ether (124; R=CH_3) was cyclized photochemically to N-norchelerythrine (125). The conversion of narcotine (126) through reduction to the alcohol (127), cyclization to the berbine (128), dehydration (129) and treatment with base gave an analogue (130) of anhydroprotopine which was similarly cyclized photochemically to the benzo- c -phenanthridine (131). The oxygenation pattern of ring D is the same as would result if capaurimine (55) were a biosynthetic precursor of a benzo-[c]-phenanthridine.



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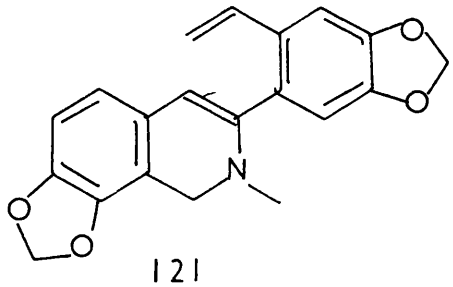

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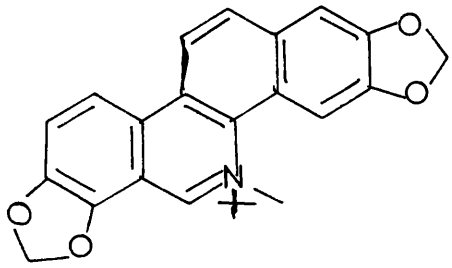

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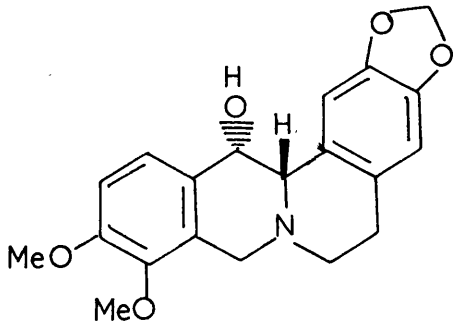

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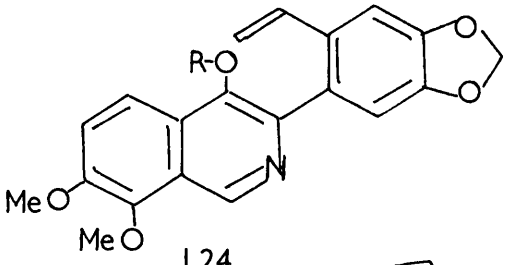

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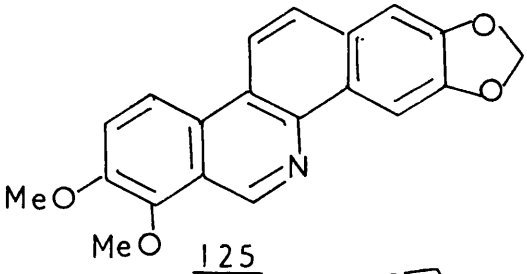

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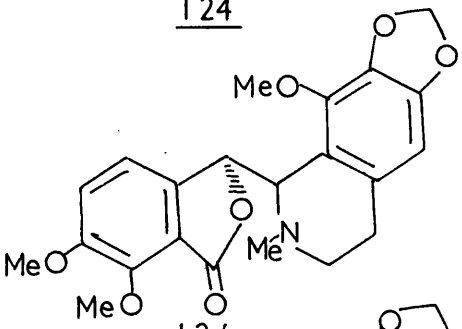

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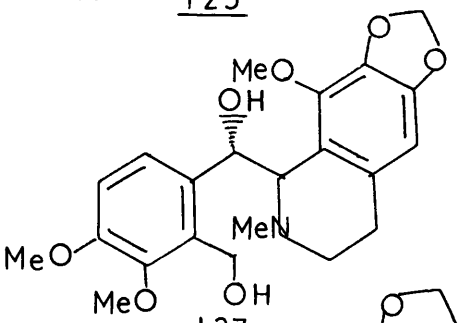

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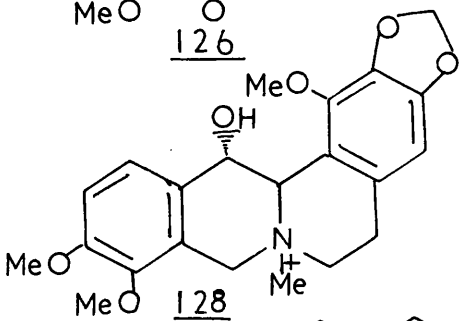

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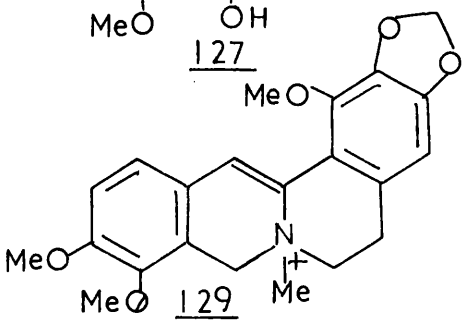

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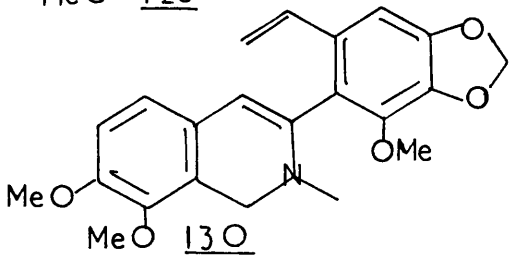

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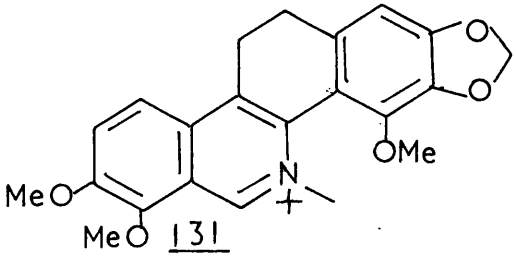
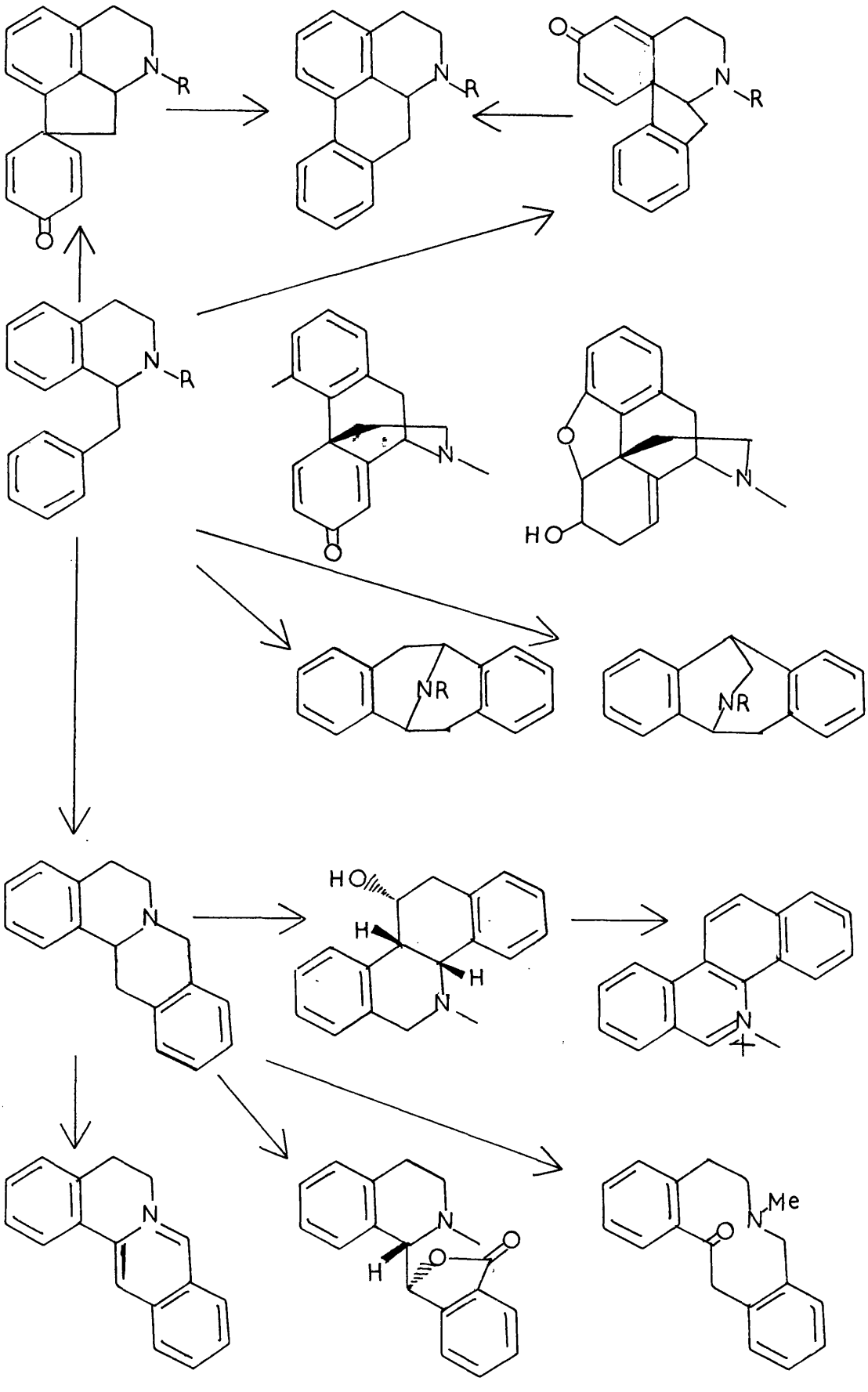


131

An excellent book on the isoquinoline alkaloids by Shamma[69] has recently become available, and includes reviews on both benzo-[c]-phenanthridines and berbines.

BIOSYNTHESIS



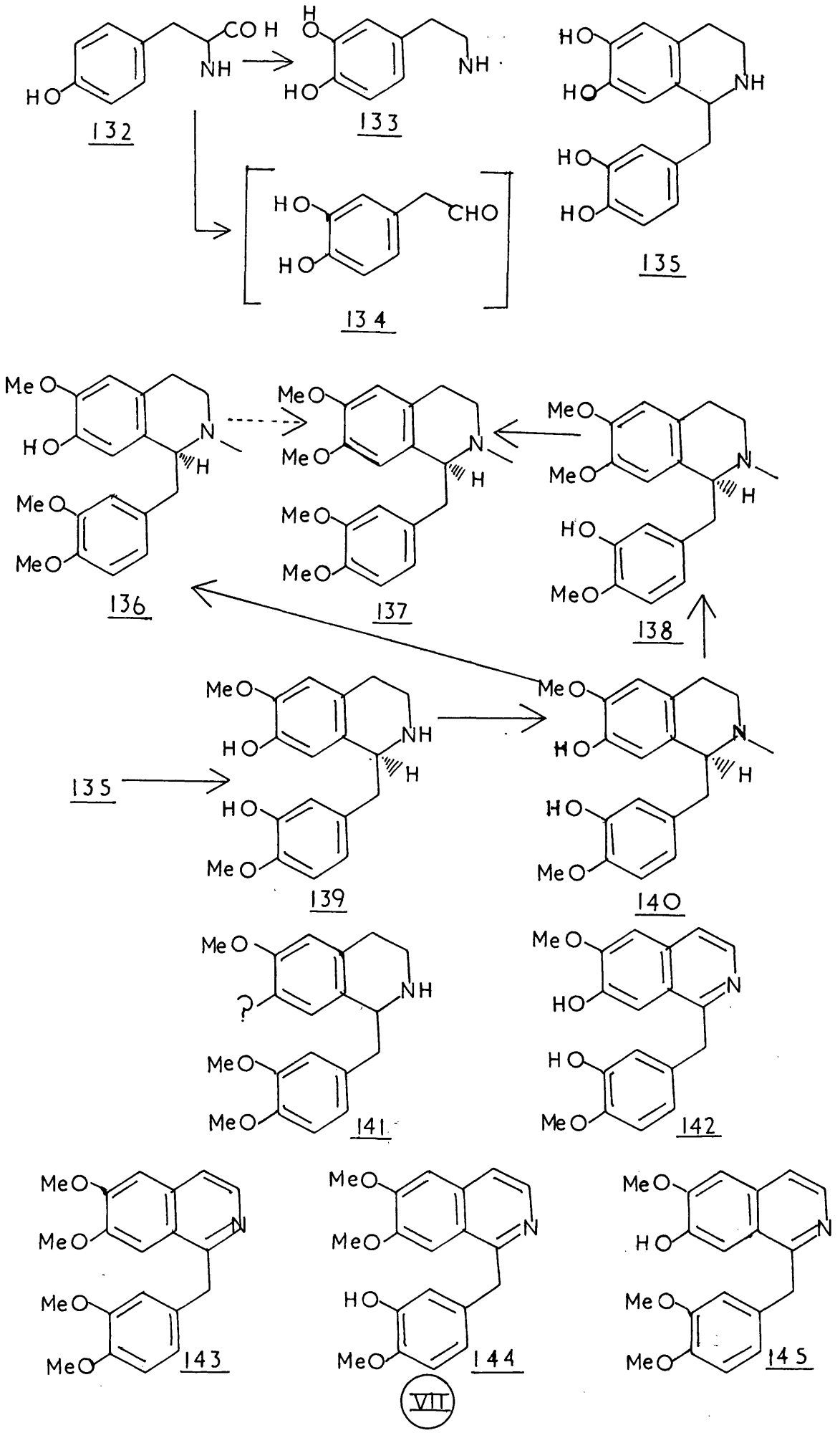
VI

The accepted inter-relationships of the various alkaloids derived from 1-benzylisoquinolines is shown in Scheme (VI).

1-Benzylisoquinolines

The general method of investigating biosynthetic pathways has been by 'feeding' plants with radioactively labelled compounds and subsequent examination of the isolated alkaloids to determine the degree of incorporation of radioactivity.[70] In addition, degradation of an alkaloid, with monitoring of the radioactivity, enables the site of labelling to be determined. Thus when tyrosine (2-^{14}C) (132) was fed to Papaver somniferum L, it was found[71] that the subsequently isolated papaverine (143) was radioactive and, by degradation studies, it was also found that labelling had occured at C-1 and C-3, approximately equally. N-Norlaudanosoline (3-^{14}C) (135) has been shown[72] to be an effective precursor of reticuline (140) and papaverine (143) in Papaver somniferum.

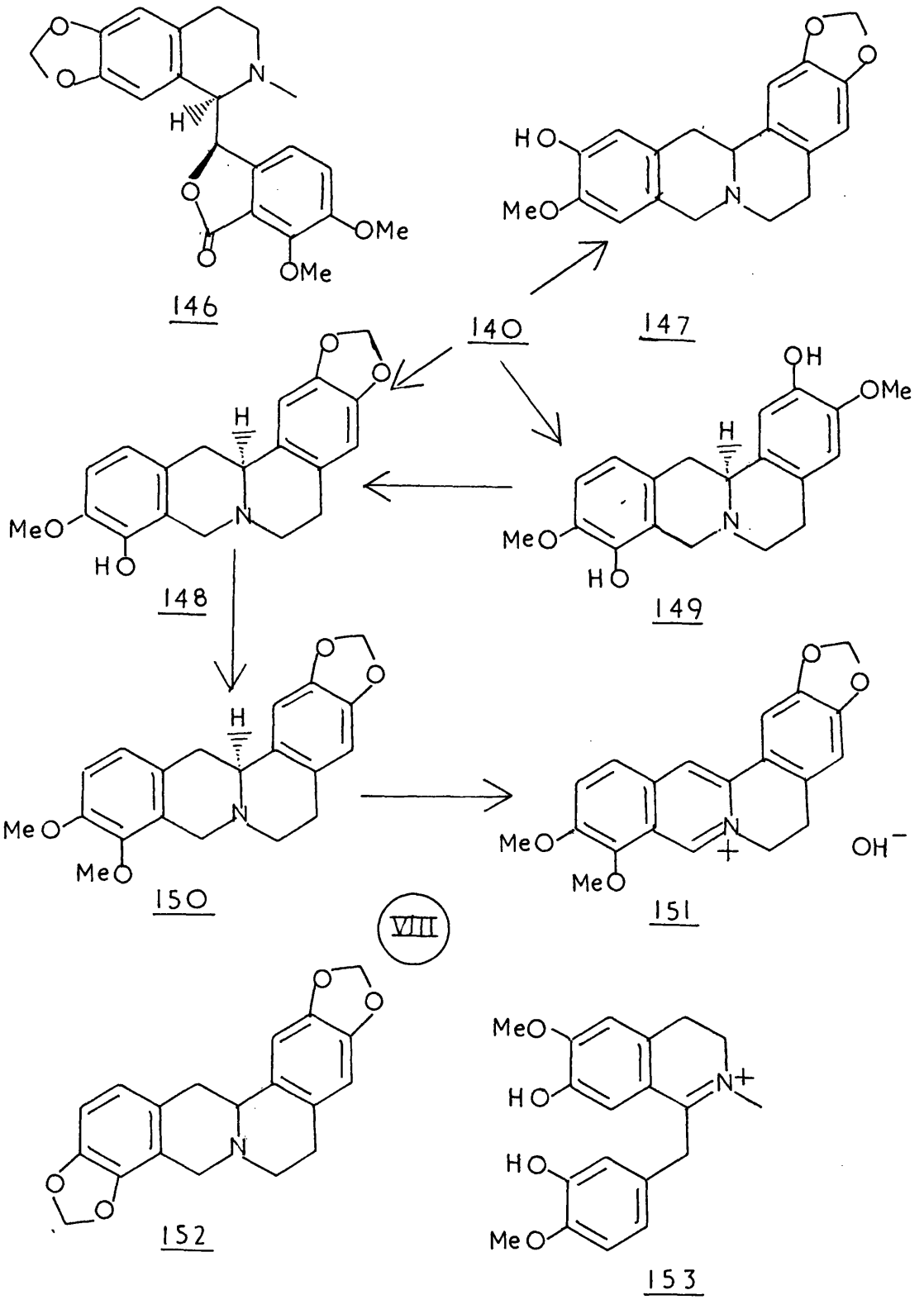
The two aromatic units that originate from tyrosine to afford 1-benzylisoquinolines are not identical.[73,74] Thus dopamine (1-^{14}C) (133) gave[75] hydrastine (146) labelled only at C-3. Since hydrastine (146) is derived from a berbine, which is in turn derived from a 1-benzylisoquinoline (vide infra), then a more detailed sequence begins to emerge. Brochmann-Hanssen et al have proposed[76] a biosynthetic scheme (VII) for the 1-benzylisoquinolines in Papaver somniferum where the key intermediate is N-norreticuline (139).



VII

Protoberberines

Tyrosine (2-^{14}C) (132) has been incorporated[77] into berberine (151), being labelled at C-6 and C-13, whereas dopamine (133) gave rise to berberine labelled[78] only at C-6 using Hydrastis canadensis L. (+) Reticuline (140) has been shown[79] to be incorporated into (-) stylopine (152), where the absolute stereochemistry at C-1 (140) and C-14 (152) remained unchanged, but the incorporation of (-) reticuline was much less efficient. Using (+) reticuline (1-^{3}H), partial loss of labelling was found, thus infering a facile and reversible reduction-oxidation process to 1,2-dehydroreticuline (22), which would then account for the incorporation of (-) reticuline into (-) stylopine (152) by reversal of stereochemistry through the iminium compound (153). (±) Reticuline has also been incorporated[80] into coreximine (154). That an N-methyl group is the source of the berbine bridge, the methylene group at C-8, was shown[81,82] by the use of reticuline (N-$^{14}CH_3$) (140). This may be compared with the cyclization[83] of N,N-dimethyl-3,4-dimethoxyphenethylamine N-oxide (155) to N-methyl-6,7-dimethoxy, 1,2,3,4-tetrahydro-isoquinoline (156). It has also been demonstrated that the methylenedioxy group in berberine (151) is derived[82] from the O-methyl group at C-6 in reticuline (140), and that the source of both the methylene group at C-8 and the methylenedioxy group in berberine (151) are derived[83] from the S-methyl group of methionine. Thus methionine is the source for both O- and N-methylation.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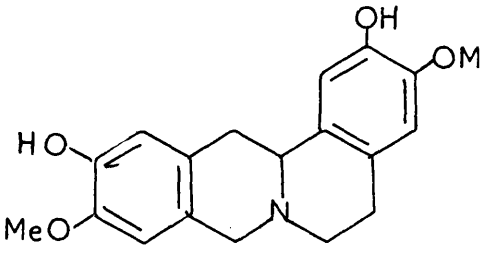

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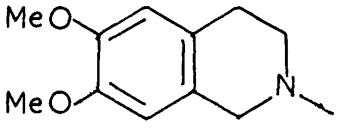

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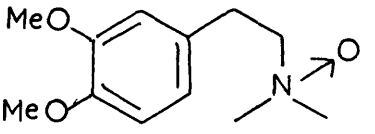

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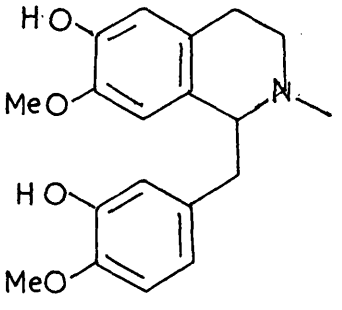

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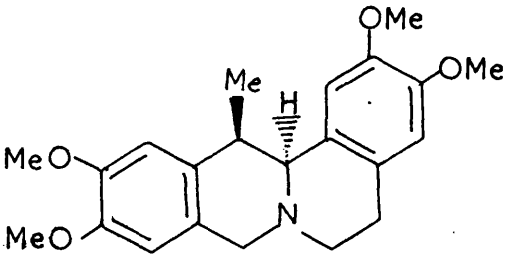

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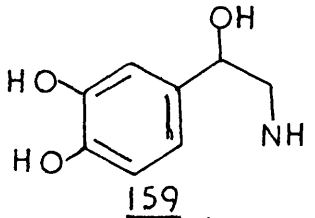

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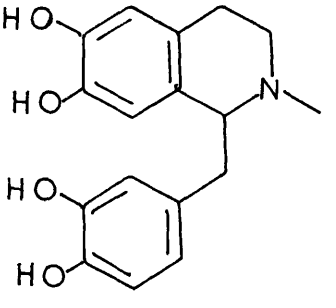

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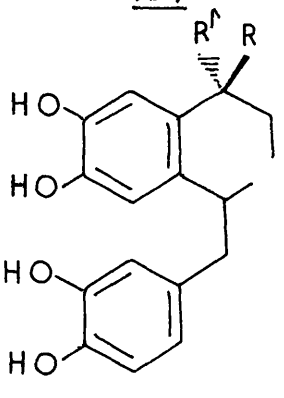

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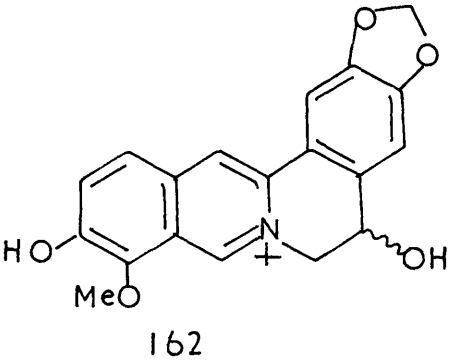


162

Protosinomenine (157) differs only from reticuline (140) in reversal of positions of the methoxyl- and hydroxyl-groups on ring A, yet it was shown[81] that protosinomenine (157) was not incorporated into berberine (151).

From such results a scheme, (VIII), has been derived[84] for the biosynthesis of protoberberines. A variety of protoberberines are known with a methyl group at C-13, and, for one of these, corydaline (158), reticuline (140) has been shown[85] to be a precursor. Since there do not seem to be any α-methylisoquinolines, it therefore appears that C-methylation occurs after cyclization to a protoberberine.

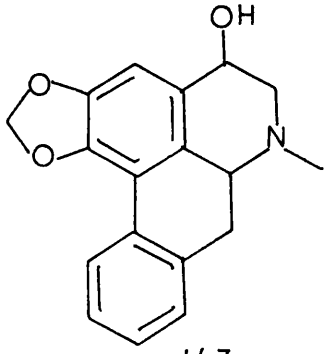
Berberastine

Only one investigation of the biosynthesis of berberastine (4) has been reported,[86] with most interesting observations. Feeding experiments with dopamine (1-^{14}C) (133) in Hydrastis canadensis L resulted in the isolation of radioactively labelled berberastine (4), berberine (151), canadine (150) and hydrastine (146). From degradation studies on berberine (151) it was shown that labelling had occured at C-5. Since berberastine (4) was found to have a higher specific activity than berberine (151) or canadine (150), then neither berberine (151) nor canadine (150) were precursors of berberastine (4). Further experiments were then carried out using ($\pm$) noradrenaline (2-^{14}C) (159) and the specific activity of the isolated berberastine (4) was reported to be far in excess of that found for (4) when using dopamine (1-^{14}C) (133). Some of the observations of Monkovic and Spenser[86] are tabulated overleaf.

	1-^{14}C dopamine hydrobromide			± (2^{14}-C) noradrenadine bitartrate		
	yield (mg.)	specific activity counts min^{-1} $mmole^{-1}$ x 10^{-4}	% incorp.	yield (mg.)	specific activity counts min^{-1} $mmole^{-1}$ x 10^{-4}	% incorp.
Berberastine iodide	3	14.2 ± 0.34	0.0024	6	396 ± 6.7	0.10
Canadine	21	12.4 ± 0.14	0.021	24	0.22 ± 0.003	0.00032
Berberine hydrochloride dihydrate	945	4.62 ± 0.03	0.29	895	0.073 ± 0.005	0.0033
hydrastine	594	0.31 ± 0.02	0.013	600	0.028 ± 0.002	0.00088
(input)	3.90	2.18 ± 0.03 x 10^5		3.94	4.43 ± 0.06 x 10^5	

Although Monkovic and Spenser exclude norlaudanosoline (135) as a precursor of berberastine (4) on the grounds that laudanosoline (160) and reticuline (140) have been shown[81,82] to serve as specific precursors of berberine (151), their results of incorporation of dopamine (1-^{14}C) do not exclude the possibility of a 1-benzylisoquinoline being hydroxylated at C-4 to provide a precursor to berberastine (4), rather than initial conversion of dopamine (133) to noradrenaline (159).

It seems reasonable to infer that berberastine (4) is derived from a 4-hydroxy-1-benzyl-1,2,3,4-tetrahydroisoquinoline, presumably 4-hydroxynorlaudanosoline (161; R=H, R^1=OH or <u>vice versa</u>). The incorporation of (±) noradrenaline (2-^{14}C) (159) into berberastine would be expected to be stereospecific, thus only one enantiomer of (161) would be expected to be incorporated unless interconversion of enantiomers of (161) occured. The incorporation of (±) noradrenaline (2-^{14}C) (159) into both berberine (151) and canadine (150) was about one sixth of that of dopamine (1-^{14}C) (133) and must be regarded as significant. Therefore a reductive process must occur, either of noradrenaline (159) to dopamine (133), of a 4-hydroxy-1-benzylisoquinoline, or, less likely, of a 5-hydroxyberbine. The principle of reversible oxidation-reduction processes of isoquinoline alkaloids has been demonstrated by the interconversion of the enantiomers of reticuline, presumably through 1,2-dehydroreticuline (153).



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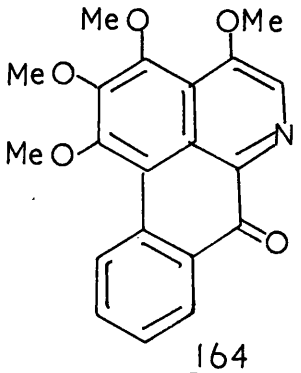

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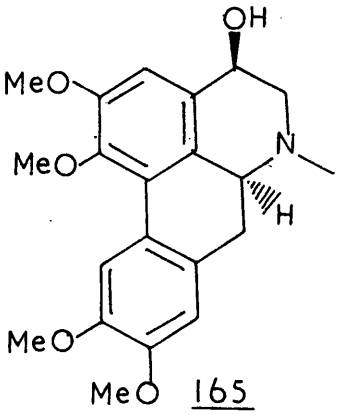

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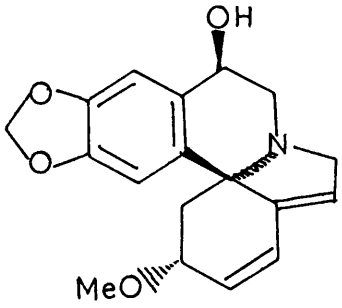

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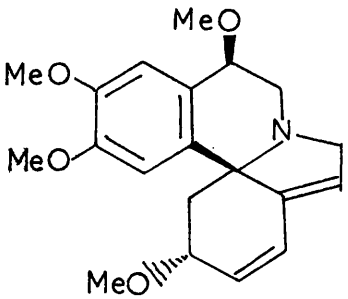

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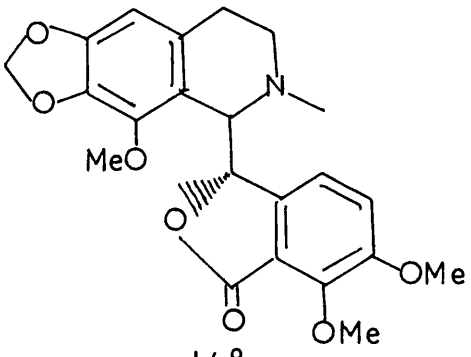

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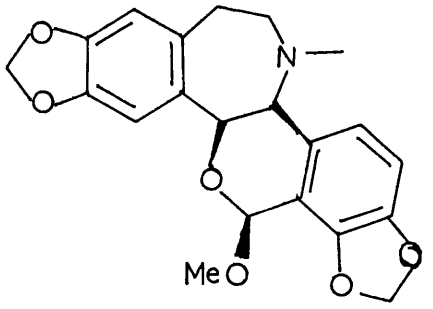

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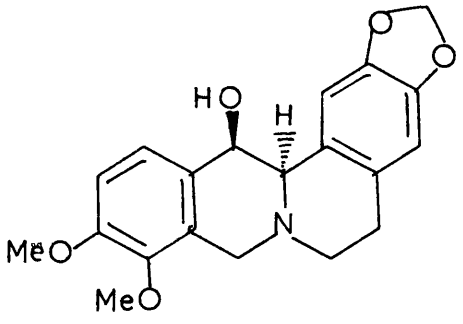

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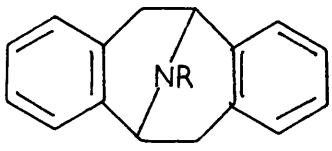
Benzylic hydroxyl groups

Besides berberastine (4), thalidastine (162) and tetrahydroberberastine, other isoquinoline alkaloids are known which bear a benzylic hydroxyl- or methoxyl-group. Such alkaloids are steporphine[87] (163), imenine[88] (164) and cataline[89] (165), erythrinine[90] (166), erthristemine[91] (167) and ophiocarpine[92] (170). One of these, imenine (164), has recently been synthesized.[93] Narcotine (168) and rhocadine (169) excemplify benzylic-hydroxylated phthalideisoquinoline and rhoeadine alkaloids respectively.

The pavine (171) and isopavine (172) groups of alkaloids, though essentially uninvestigated biosynthetically, are presumed[94,95,96] to arise from 1-benzylisoquinolines. It has been suggested by Stermitz and Seiber[95] that the pavines are biosynthetically derived from reticuline (140) by oxidation to 2,3-dehydroreticuline (173) but this is regarded as improbable. If, as was suggested,[95] 1,2-dehydroreticuline (153) is in equilibrium with 2,3-dehydroreticuline (173) then, since reticuline is the precursor of the principle alkaloids of Papaver somniferum, significant amounts of products from (173) might be expected, namely pavines, but this is not so. Of course, the lack of a potential product in a biosynthetic sequence may be attributed to the lack of the appropriate enzyme in the plant under consideration but, in the laboratory, the conversion of compounds of type (173) to pavines is facile.[97,98,99]

Reaction of 4-hydroxy-1-benzyl-1,2,3,4-tetrahydroisoquinolines (174) in aqueous acids has readily given both isopavines[100,101] and pavines,[102] and it has been suggested[31] by Dyke et al that isopavines may be biosynthetically derived in an analogous manner, from 4-hydroxylated isoquinolines. In the synthesis of an isopavine, for a concerted displacement of the 4-hydroxyl-group of (174) by the 1-benzyl group, a 1,4-'trans' stereochemical system would be required, eg. (175), but stereochemistry would be unimportant for a reaction involving a benzyl carbonium ion, eg. (176). The pavines (171) arise by dehydration of the benzylic alcohol (174) to a 1,2-dihydroisoquinoline (178), which, on protonation at C-4 affords a '2,3-dehydroisoquinoline' such as (173). Such intermediates readily rearrange to 3-benzyl-3,4-dihydroisoquinolines (179) and subsequently cyclize to pavines (43).

If the stereochemistry of a 4-hydroxy compound were as in the trans example (175), then antiperiplanar dehydration would result in loss of the 1,3-cis hydrogen, relative to the 1-benzyl group, whereas formation of the enamine (178) from the carbonium ion (176) need not be stereochemically controlled. If enzymatic hydroxylation at C-3 of a compound such as reticuline (140) were to occur to produce the hypothetical 3-hydroxyreticuline type (180), then a compound analogous to the suggested[95] 2,3-dehydroreticuline (173) would be produced, and direct cyclization would require trans-stereochemistry and the 1,3-cis hydrogen would be retained. If such a compound as (180) were produced, it could also be dehydrated to (173), and then the stereochemistry of hydroxylation would be unimportant.



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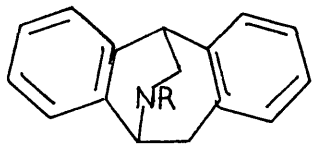

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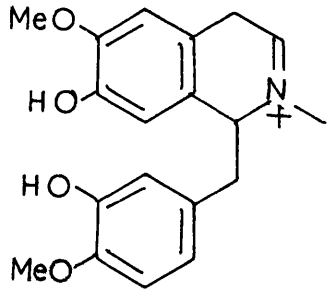

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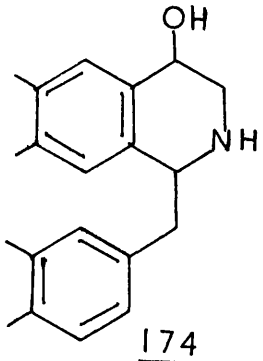

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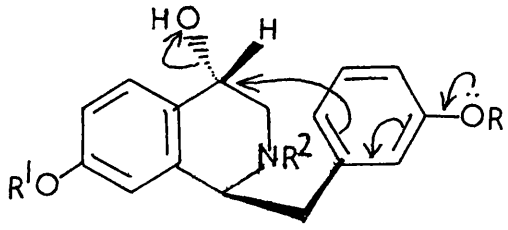

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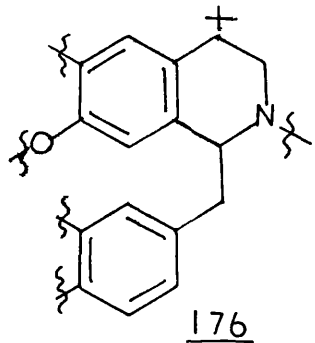

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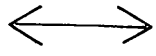

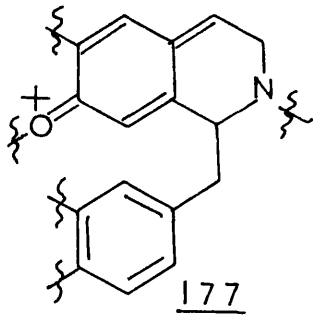

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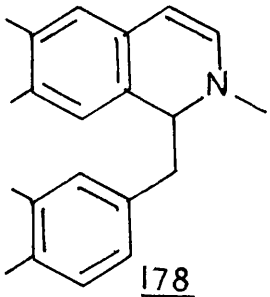

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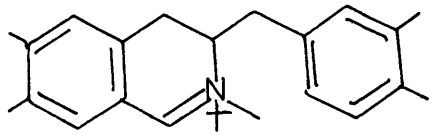

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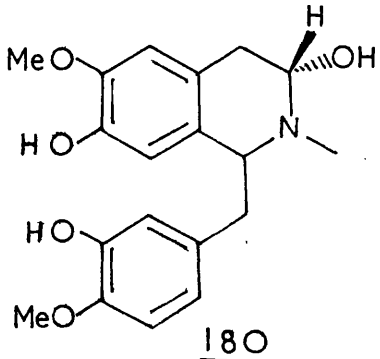

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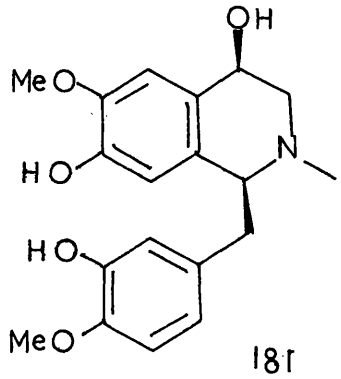

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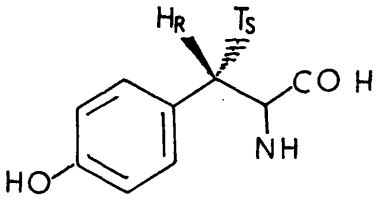
It would be interesting to know the absolute configuration at C-5 of, for example, Berberastine, and to compare this with the absolute configuration of isopavines. If the absolute configurations were the same, then it might suggest only one stereochemical course of hydroxylation of, for example, dopamine. The biosynthetic production of pavines might conceivably arise from, for example, a 1,4-cis-hydroxy-compound such as (181).

Many of the possible biosynthetic routes to pavines and isopavines could well be investigated by using chirally labelled tyrosine (3-^{3}H) (132) (182). This reagent has already been used in feeding experiments[103,104] to ascertain the course of hydroxylations in the biosynthesis of haemanthamine (184) and it was shown that hydroxylation at C-11 occurs with retention of configuration. This is regarded as the normal course for hydroxylation at a saturated carbon atoms.[105,106] Since oxycrinine (185) is an intermediate[103] in the biosynthetic sequence to haemanthidine, hydroxylation does occur at a saturated carbon, in contrast to the benzylic carbon site for the proposed intermediate to isopavines.

An as yet hypothetical biosynthetic intermediate such as 4-hydroxy-norreticuline (186; R=OH) warrants consideration as a precursor to the aromatic 1-benzylisoquinolines such as papaverine (143). In a series of feeding experiments with labelled precursors, Brochmann-Hanssen et al have shown[76] that norreticuline (139) is a precursor of papaverine (143). It was earlier mentioned that both benzylic hydroxylation and reduction must occur in Hydrastis canadensis, due to the



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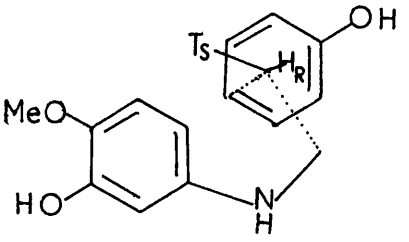

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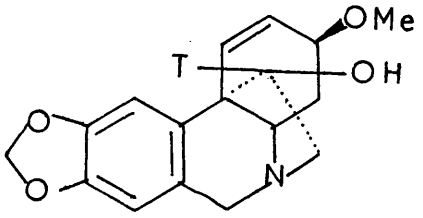

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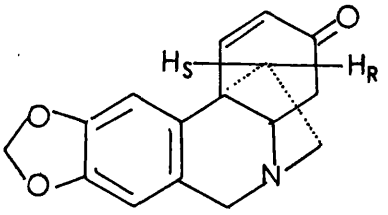

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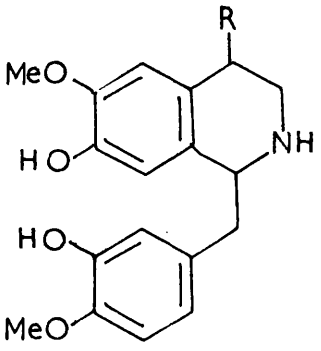

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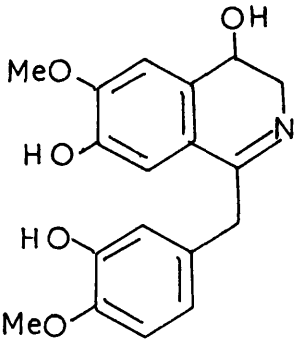

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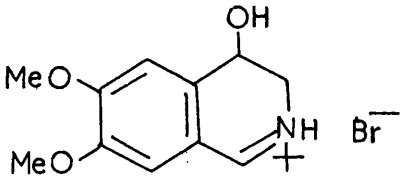

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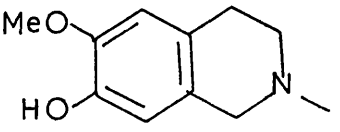

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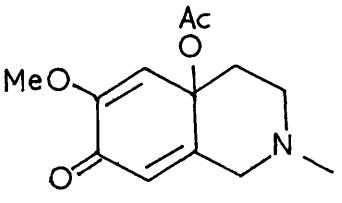

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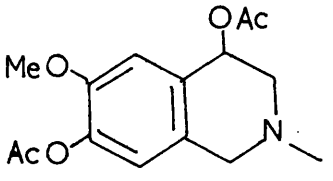

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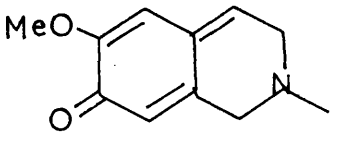

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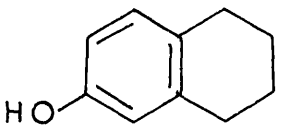
successful incorporation of both dopamine (1-^{14}C) and noradrenaline (2-^{14}C) into both berberine (151) and berberastine (4). It certainly seems possible, therefore, that norreticuline (186; R=H) may be hydroxylated to 4-hydroxy-norreticuline (186; R=OH). Since the enantiomers of reticuline are presumed to interconvert through 1,2-dehydroreticuline (153), such a process on 4-hydroxy-norreticuline (186; R=OH) would afford (187), which needs only dehydration and O-methylation to obtain papaverine (143). Little attention appears to have been given to the process by which a 1-benzyl-1,2,3,4-tetrahydroisoquinoline is biologically aromatized; such aromatizations of tetrahydroisoquinolines can prove extremely difficult in the laboratory - except for 4-hydroxy-1,2,3,4-tetrahydroisoquinolines. The latter compounds are aromatized most readily[107] by, for example, initial oxidation with N-bromosuccinimide to 4-hydroxy-3,4-dihydro-isoquinolines (188) and subsequent acid-promoted dehydration.

Examples of laboratory hydroxylations at C-4 of 7-hydroxy-1,2,3,4-tetrahydroisoquinolines are known. Treatment of corpalline (189) with lead tetraacetate affords[108,109] the quinol acetate (190), which is susceptible to acid-induced rearrangement to 4,7-bisacetoxy-6-methoxy-1,2,3,4-tetrahydro-isoquinoline (191). This compound presumably arises through the quinone methide (192), and is highly susceptible to nucleophilic displacements under basic conditions[110,111] to obtain 4-substituted derivatives of corpalline (189). The reactive species is again presumably the quinone methide (191). This might at first be considered at variance with the related

example[112] of oxidation of 6-hydroxytetralin (193), where the intermediate quinol acetate (194) gave 5,7-bisacetoxy-tetralin (195), but 6-hydroxytetralin has also been oxidized to 6-hydroxytetralene[113] (196) and 1-methoxy-6-hydroxy-tetralin (197).

The oxidation of an isoquinoline to a quinol acetate has been extended[114] to the oxidation of codamine (198). Although the initial product of oxidation with lead tetra-acetate was not reported as characterized, it is reasonable to suppose that it was the quinol acetate (199). This was then subjected to similar acid conditions that induced the rearrangement of the simpler quinol acetate (190) to the 4-acetoxy derivative (191), and both (±) O-acetylthaliporphine (200; R=H, R=OAc) (14%) and (±) 4-acetoxy-O-acetyl-thaliporphine (200; R=R^1=OAc) (6%) were obtained. Unfortunately it was not clear whether cyclization occured through the quinone methide (201) or the carbonium ion (202). The (±)-4-acetoxy-O-acetylthaliporphine (200; R=R^1=OAc) presumably arose due to oxidation of (200; R=H, R^1=OH) with lead tetraacetate, since the reported procedures did not exclude excess lead tetraacetate. The authors, Umezawa et al, favoured a "Michael-type addition of the 6-position in the veratryl group to the 9-position in (199), and a concerted elimination of the 10-acetoxy-group, followed by a 1,2-shift of the C-6' C-9 bond to the 8-position, and aromatization."



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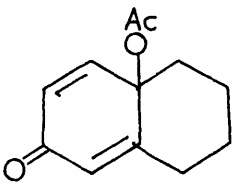

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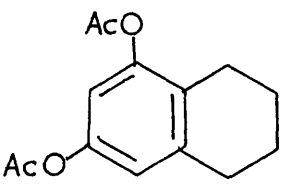

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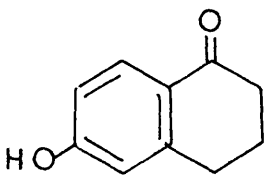

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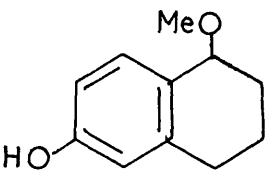

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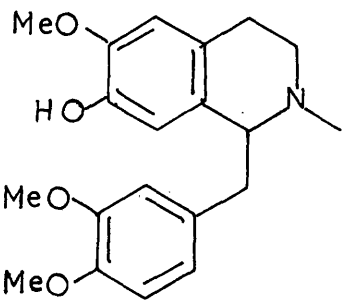

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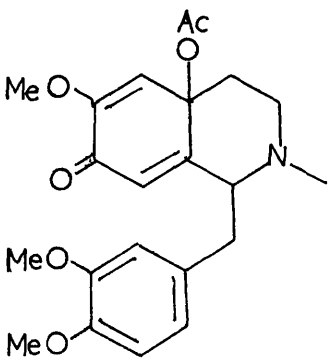

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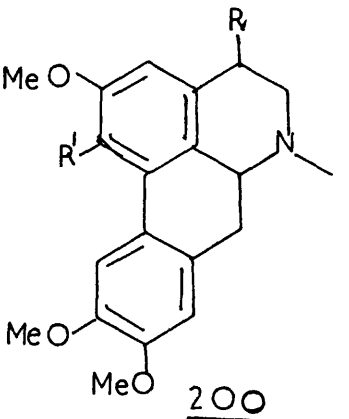

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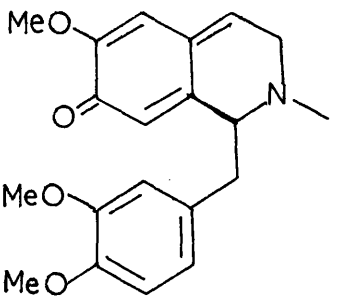

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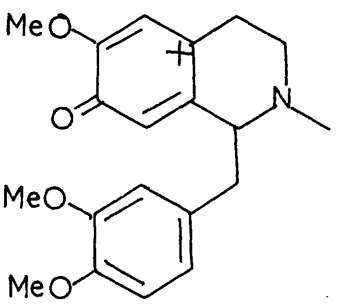

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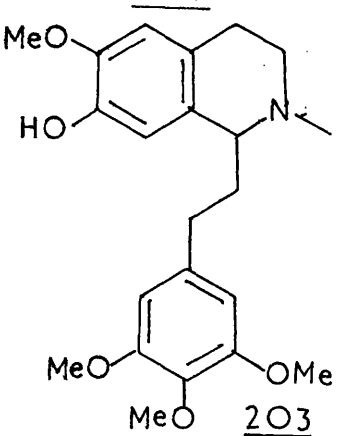

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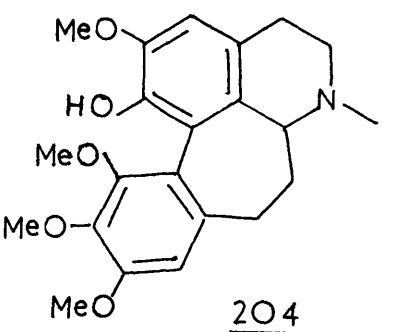

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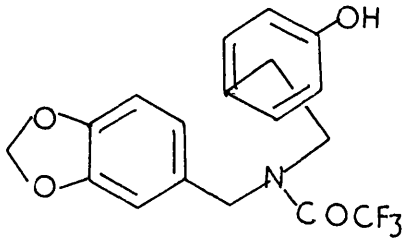
By a similar oxidation of N-methyl-1-(3,4,5-trimethoxy-phenethyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (203), the homoaporphine Kreysigine (204) has been synthesized.[115]

Although the oxidant lead tetraacetate is generally considered to be a radical oxidant, the intermediates to both cyclizations to (±) thaliporphine (200; R=H, R^1=OH) and (±) kreysigine (204) have been subjected to a two-electron oxidation[116,117] prior to cyclization. Two-electron oxidations with thallium (III) trifluoroacetate (TTFA) have recently been employed by Schwartz et al to accomplish intramolecular phenolic coupling.[118] Reaction of the N-trifluoroacetyl amine (205) with TTFA in dichloromethane afforded the dienone (206) (19%), which, on hydrolysis, gave (±) oxocrinine (185). An analogous oxidation of (207), a similar 1-phenethyl-isoquinoline as that used for the synthesis of kreysigine (204) but where the amine function is protected as a borane, gives, after amine deprotection, (±)-O-methylandrocymbine (208). The reaction is formalized in the sequence (209) (210) (211) to illustrate the probable carbonium ion at C-10. It would then appear that annelation of (203) to kreysigine (204) may not proceed through the carbonium ion (211), but, in view of the low yields in the syntheses of both kreysigine (204) and O-methylandrocymbine (208) it would be incautious to draw such mechanistic conclusions from available evidence. In both cases, the bulk of the reaction product was unaccounted for.

Although comment has been made regarding the low yields of the above mentioned cyclizations, such yields are far



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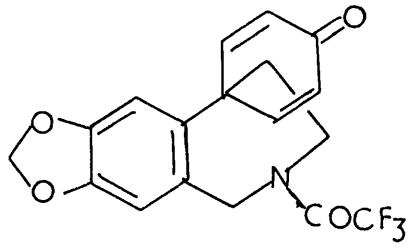

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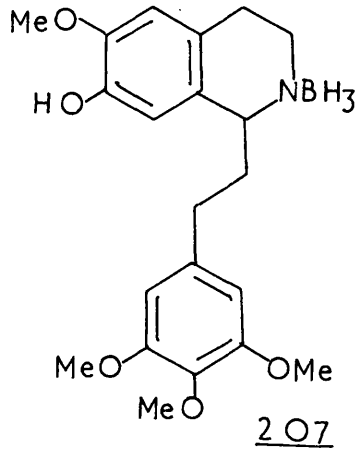

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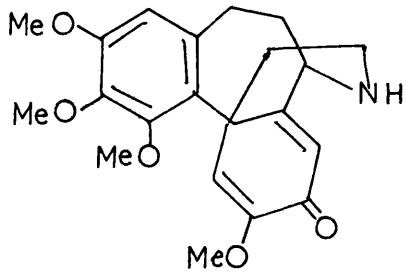

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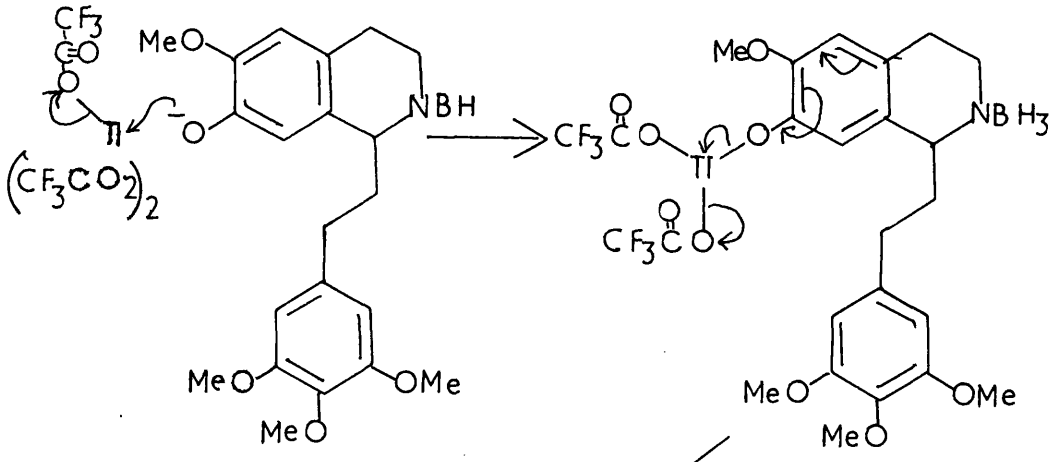

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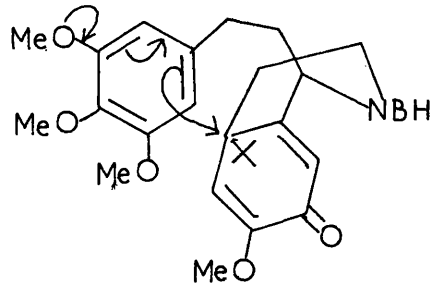

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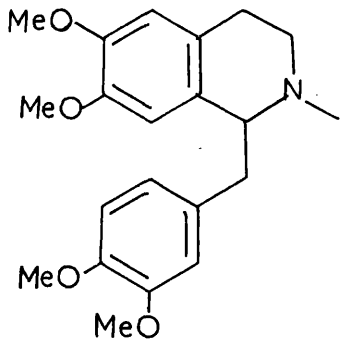
superior to those commonly obtained in phenolic cyclizations induced by one-electron oxidants.[119] Exceptional yields in phenolic cyclizations have been obtained using vanadium (V) oxychloride,[120,121] and the electro-oxidative cyclization of laudanosine (212) to O-methyl flavinantine (213) has been accomplished[122] in 52% yield.

A major contribution towards the understanding of the inter-relationships of the isoquinoline alkaloids was the paper by Barton and Cohen[123] on some biogenic aspects of phenol oxidation. The pattern of inter-relationships expounded in that paper has been of great value, but it was stated or presumed throughout that the coupling mechanism was of a radical type. From a recent review[119] of the topic of phenolic oxidation of isoquinolines it is obvious that a great deal of effort by many research workers has gone into attempts to duplicate oxidative biosynthetic reactions in the isoquinoline field by one-electron oxidations of phenols. The generally - but not invariably - abysmal yields could well reflect a basic error of assumption - that biosynthetic oxydative cyclizations are radical in character. It could well be that the biosynthetic pre-cyclization intermediates are ionic in character.

In a biological system, oxidative stages are promoted by enzymes, and the investigation of proposed biosynthetic pathways by use of enzymes or enzyme extracts is becoming increasingly popular. Because of the considerable difficulties attending the isolation of an enzyme, there is naturally a tendency to use an already characterized enzyme whose properties are estimated to parallel those of the unidentified plant enzyme.



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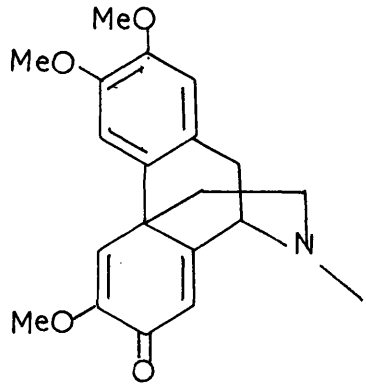

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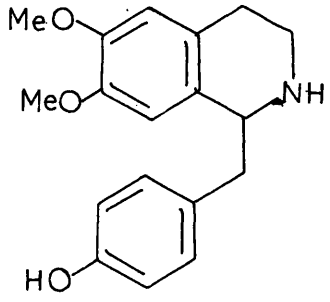

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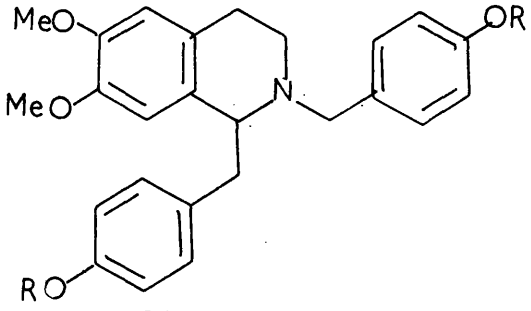

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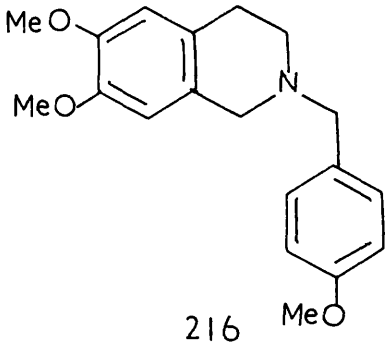

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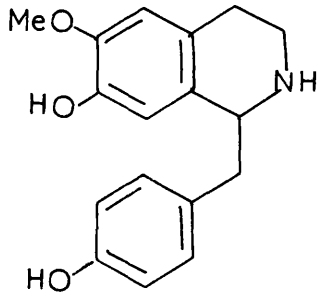

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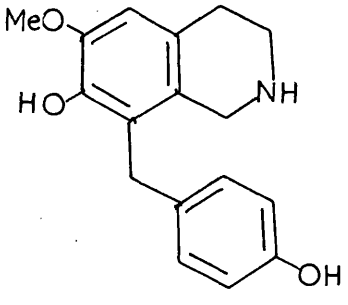

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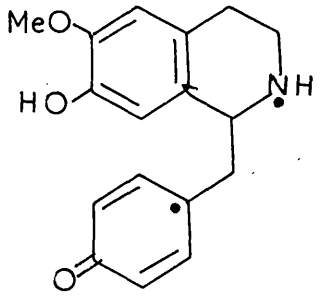

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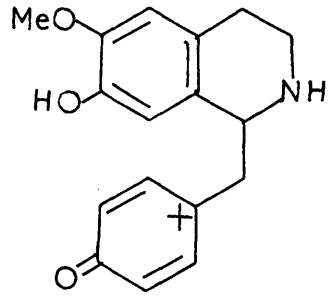
For example, oxidation of dl-N-norarmepavine (214) with crude horse-radish peroxidase, was reported[124] to give both 1,2-dianisyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (215; R=CH_3), the corresponding diphenol (215; R=H), and o-methylsendaverine (216). Similar oxidation of dl-N-methylcodaurine (217) gave a bis-benzylisoquinoline, and, after reductive work-up, corpalline (189) and the 8-benzylated isoquinoline (218). It was assumed by the authors that the oxidative rearrangement was by means of a diradical, eg. (219). Instead, the carbonium ion (220) could then afford the quinone methide (221), and result in transfer (222) of the 1-benzyl group to nitrogen with concommitant formation of a $\Delta^{1,2}$ bond. Alternatively, elimination of the benzyl carbonium ion (224) could then give 1,2-dehydro-N-norcorpalline (223) and the highly labile quinone methide (225). Enzymic phenolic oxidation of reticuline (140) has given[125] a 4% yield of α-hydroxyreticuline (226; R=H), and rearrangement[126] of (226; R=Me) gave a small (3%) yield of the ring-expansion product (227). The latter product could be explained through an aziridinium intermediate (228), similar to (222), but with cleavage of the original C^1-C^2 bond rather than benzylic migration. In this context it is interesting to note the isolation of the unusual analogue[127] of a bis-benzylisoquinoline which contains a benzazepine ring (229).

As part of a series of studies of peroxidase action, some observations of the oxidation of 4-alkyl-2,6-dimethylanilines *et al* by horseradish peroxidase have been reported.[128] In the case of 2,3,4-trimethylaniline (230), the two products



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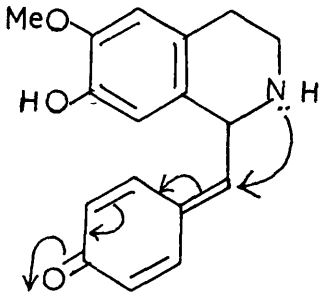

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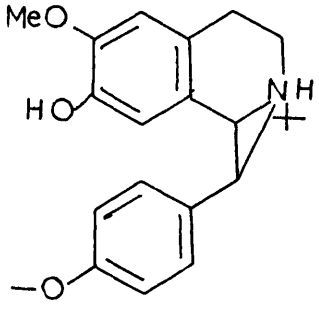

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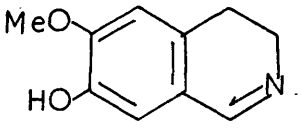

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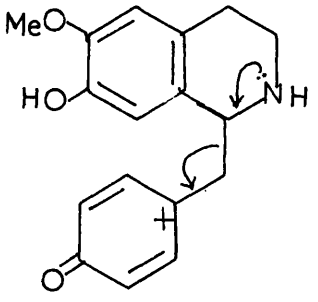

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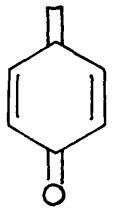

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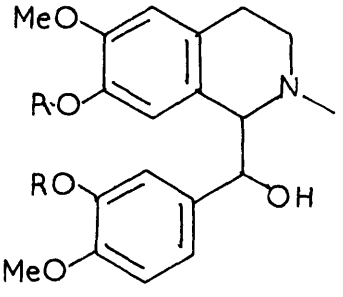

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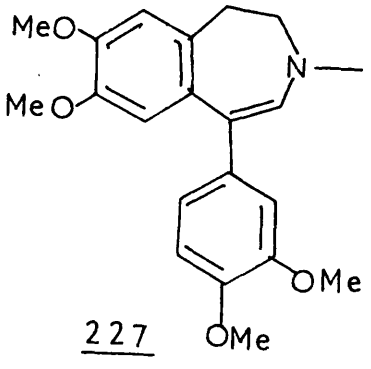

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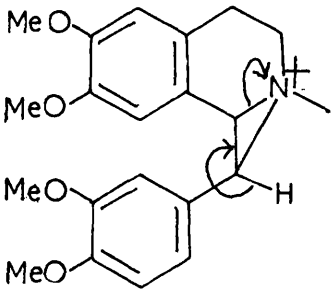

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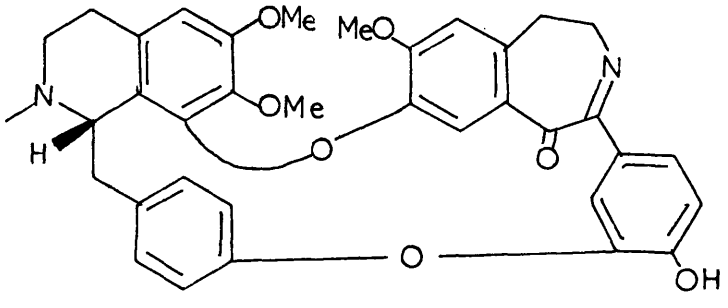

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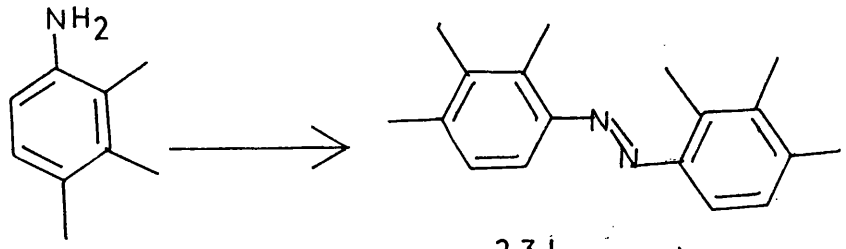
identified were 2,3,4,2',3',4'-hexamethylazobenzene (231) and 2,3,5-trimethyl-p-benzoquinone-4-(2',3',4'-trimethyl)anil (232). The former compound (231) might be explained by radical "head to head" coupling or by "head to head" dimerization of a quinone methid imine, but the latter product (232) requires migration[129] of a methyl group. For 4-t-butyl-2,6-dimethylaniline (233) the main product is 2,6-dimethyl-p-benzoquinone-4-(4'-t-butyl-2',6'-dimethyl)anil (234; R=H) where intermediacy of a p-quinone methid is not possible and the minor component was the product of migration of a t-butyl group (234; R=t-Butyl). These observations may be explained by the use of oxidation to a carbonium ion, eg. (235). Attack by nitrogen of a second molecule of unoxidized compound (233) then gives rise to the required coupling (236) and migration of, or elimination of, the 4-alkyl group would then afford the reported products (234; R=H) and (234; R=t-butyl). For 2,3,4-trimethylamine (230), the initial carbonium ion (238) could generate a quinone methide imine (239), and, by for example "head to head" dimerization (240), the azobenzene (231) would result.

In a study of the biosynthesis of some of the apparently directly coupled aporphines, it was found[130] by Battersby et al that the best precursor of corydine (240), glaucine (241) and dicentrine (242), from a wide range of studies, was the 6-hydroxy compound, norprotosinomenine (243). It was therefore postulated that initial annelation was to give a dienone of type (244; R=OH, R^1=H, or R=H, R^1=OH) R^2=H or Me). Such dienones (R=OH, R^1=H, R^2=CO_2Et or $COCF_3$) have been obtained[131]



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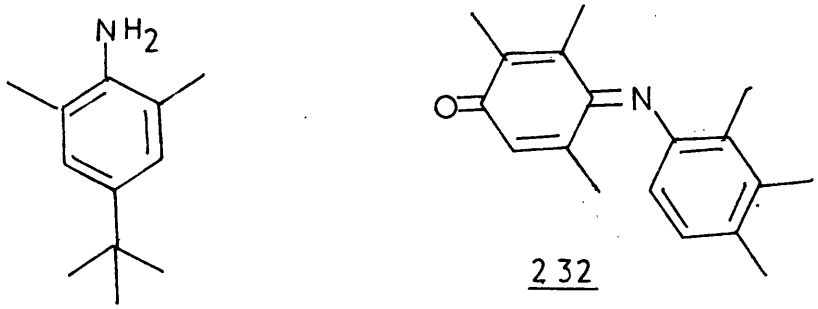

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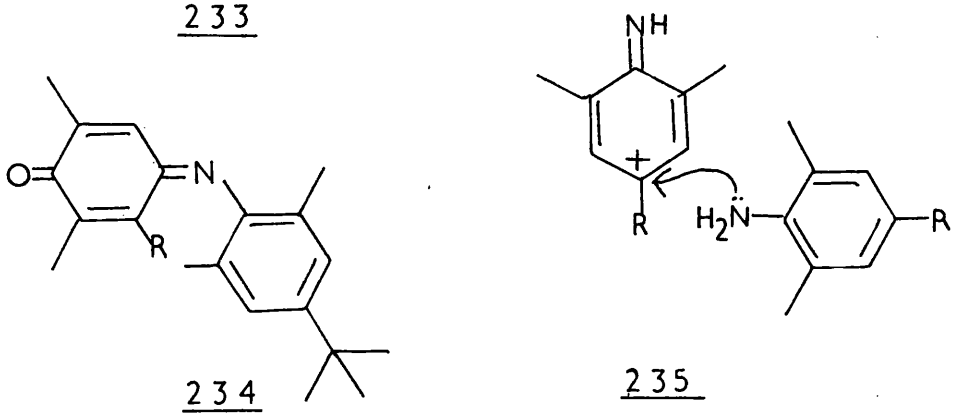

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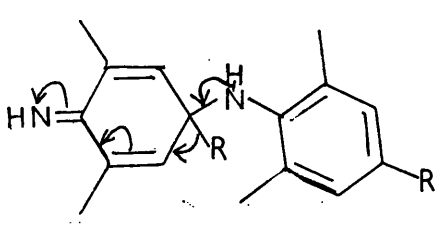

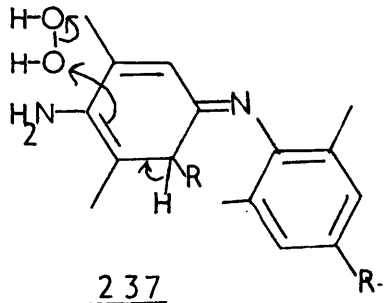

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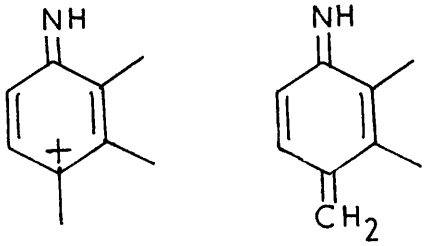

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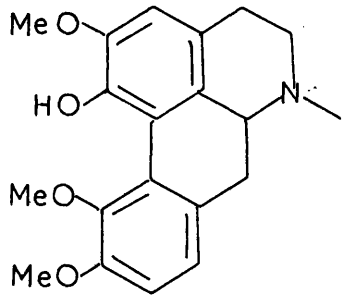

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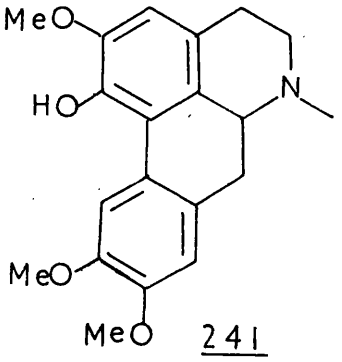

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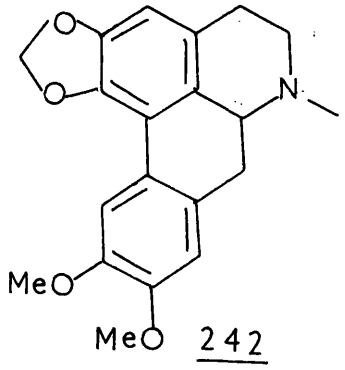

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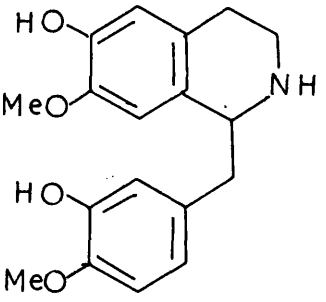

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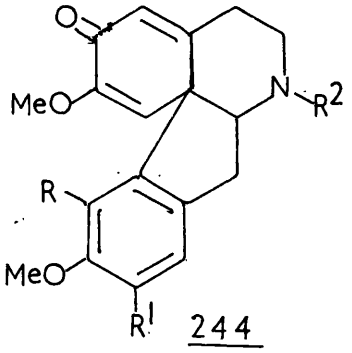

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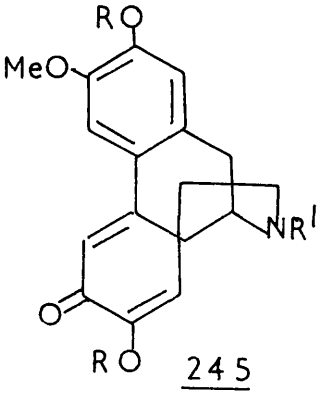

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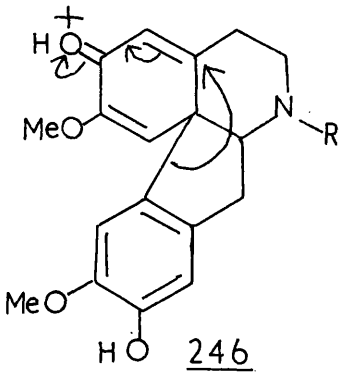

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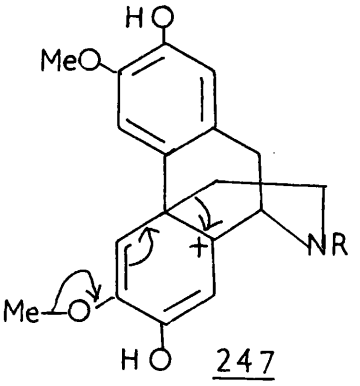

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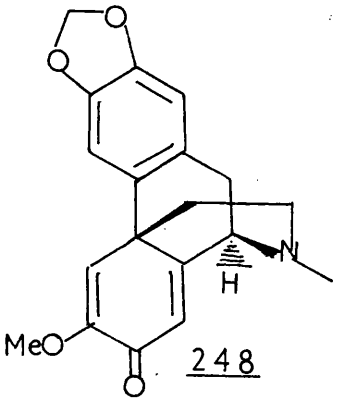

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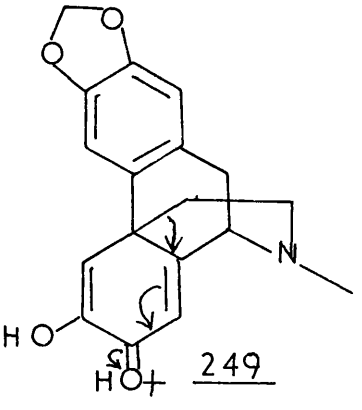
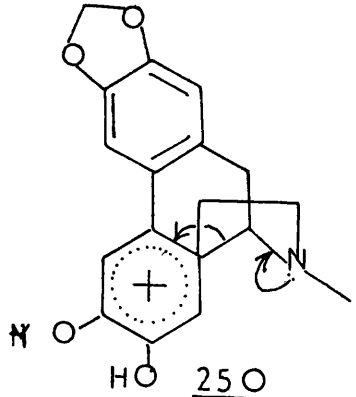


249

by ferricyanide oxidative coupling of the corresponding 1-benzylisoquinolines. Attempted acid-catalysed rearrangements of these dienones did not, however, yield aporphines but gave, after methylation, the dienones (245; R^1=CO_2Et or $COCF_3$, R=Me). It should be noted that cleavage of the "$C^{2'}$-C^9" bond must have occured, along with cleavage of the C^4-C^{10} bond, since the benzenoid part of the isoquinoline has been rotated through 180° along the C^9-C^6 axis. If rearrangement by aryl migration of the protonated species (246) occured, then a carbonium ion would be generated, and demethylation would then afford the morphinanedienone (247). Further protonation could then generate the carbonium ion (247), and alkyl migration would then afford the dienone (245). This may be compared with the acid-promoted conversion[132,133] of amurine (248) to 1,2-dihydroxy-4- -N-methylaminoethyl) 6,7-methylenedioxyphenanthrene (253), where it has been suggested the intermediate (250) is formed in an analogous manner to (245) from (247), and is further fragmented to (253) by the sequence (250)→(251)→(252). Presumably then, the dienone (245) does not further break down as in (250) to (251) due to the phenolic group at C-2 where an extended conjugation system (254) may be promoted.

The reactions of 2-bromoisophorone[134] (255) warrant a comparison with some of the annelations of 1-benzylisoquinolines. Thus, treatment of (255) with nucleophiles affords 2,3,5- and 3,4,5-trimethylphenol, where a methyl from the gem-dimethyl group can migrate in either direction. This may be compared with the presumed biosynthetic conversion of norprotosinomenine



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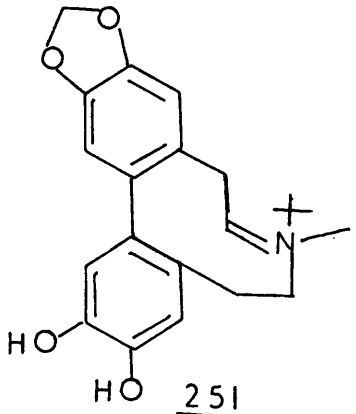

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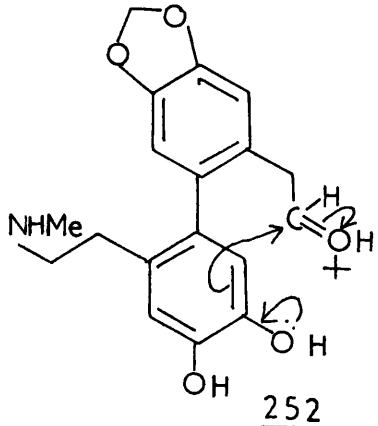

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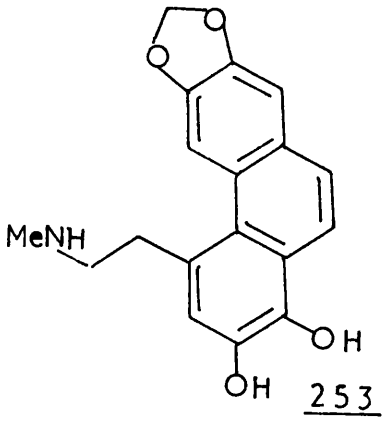

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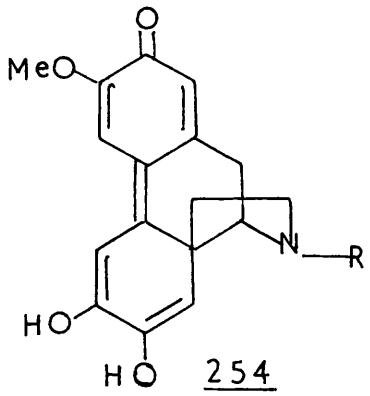

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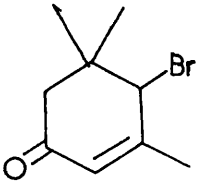

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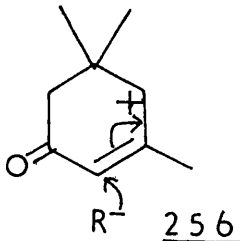

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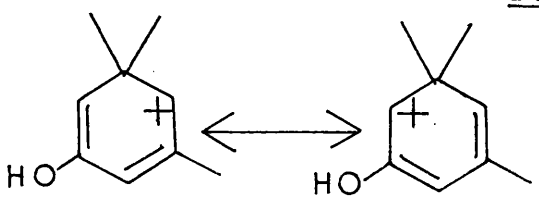

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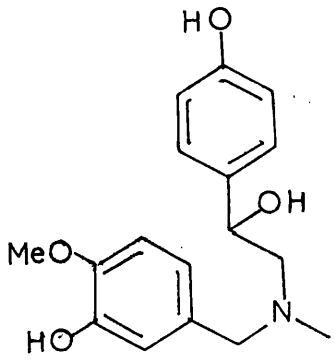

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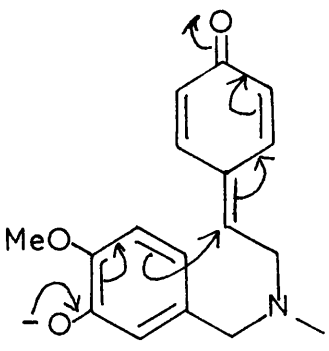

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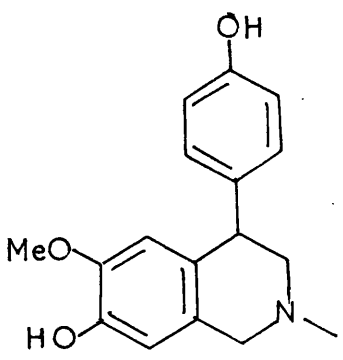


261

(243) to aporphines, and the chemical conversion of (244) to (245). Also, substitution does not occur directly at C-2 but at C-4, and this may be compared with the direct biosynthesis of aporphines from reticuline (vide infra).

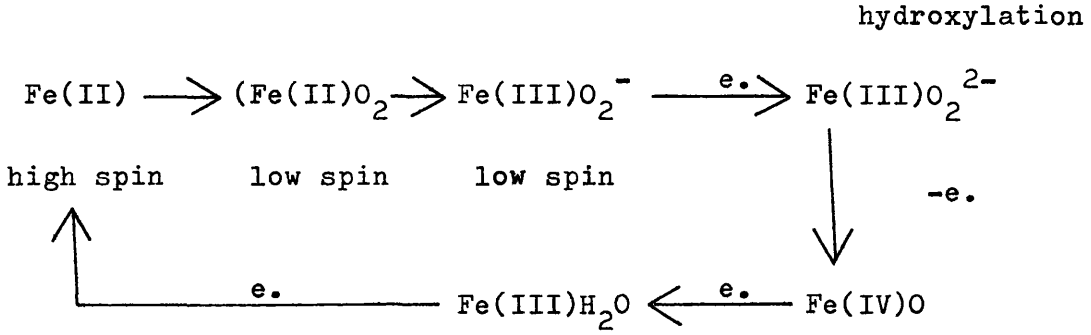
Enzymes

Although various speculations regarding the nature of the process of oxidative couplings of 1-benzylisoquinolines have been made, little consideration has been given to the enzymes which promote such couplings. A great deal of valuable work has been done, both 'theoretical' and synthetic, on the assumption that the coupling processes are by means of radical intermediates and generally diradicals have been proposed as the precursors to cyclizations. In the early studies of the use of crude enzyme extracts these assumptions seemed to be valid since the 'oxidase' enzymes used appeared to be of a radical type since they were diamagnetic. For example, cytochrome P-450 is diamagnetic and at first it was presumed to be a one-electron oxidant, due to the sequence:-

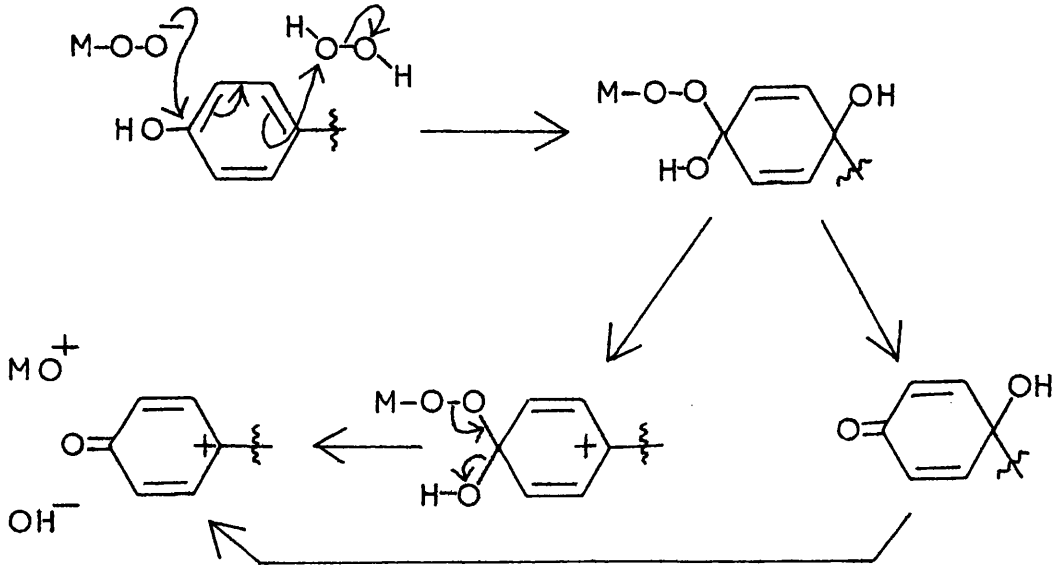
$$Fe^{3+} \longrightarrow Fe^{2+} + e.$$

It was then assumed that the oxidative power was due only to this one electron change, thus being a radical, one electron, oxidant. This assumption has now been shown[135,136] to be in error and such oxidants as cytochrome P-450 (eg. from liver extracts) and horseradish peroxidase are in fact multielectron oxidants where successive one electron oxidation changes are

"stored" by an oxygen molecule, eg.



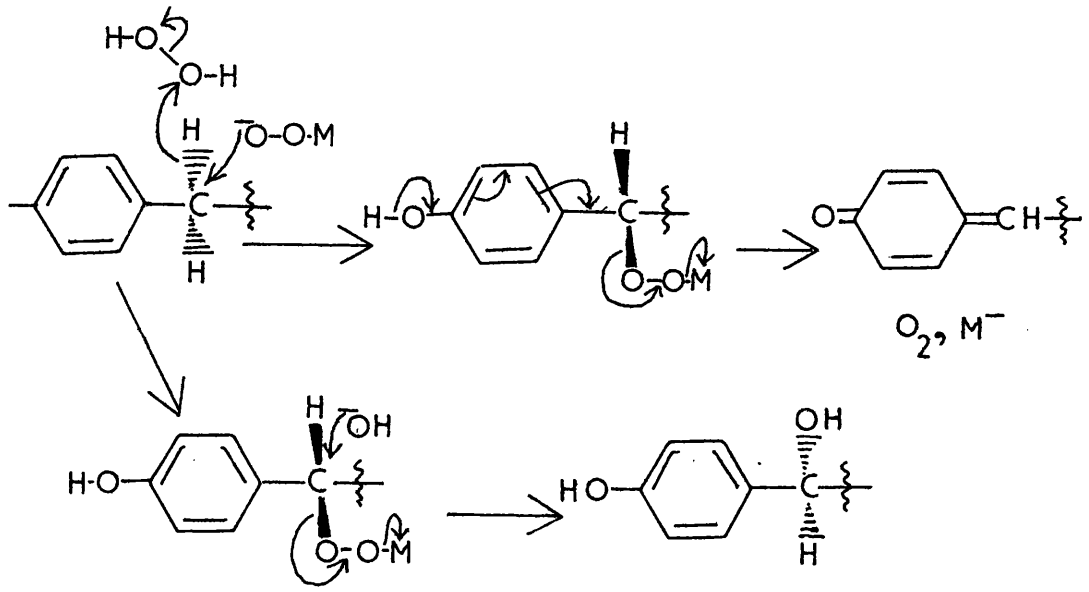
Thus the effective oxidant is probably O_2^{2-} rather than Fe(III) . Thus the following oxidative sequence may be envisaged for a phenol:-



Scheme 1

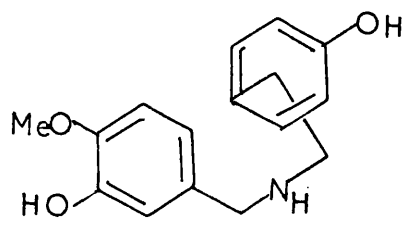
Thus if M is Fe(III) , then MO^+ is $Fe(III)O^+$ ie. Fe(IV)O .

Alternatively, when a suitable 4-alkylphenol is considered:-



Scheme 2

Thus either a benzylic alcohol and/or a quinone methide may be generated and benzylic protonation of a quinone methide then gives the same carbonium ion as in the direct phenolic oxidation scheme. Obviously it would be highly desirable to determine which of these two schemes operates for any particular annelation of a 1-benzylisoquinoline and for any other related phenolic oxidation where benzylic oxidation is also possible. In the discussion of the biosynthesis of pavines and isopavines mentioned earlier, the possible application of tyrosine (3-^{3}H) as a biosynthetic probe was mentioned. This reagent could well be used for a general reinvestigation of the biosynthesis of isoquinoline alkaloids to determine whether Scheme (2) is of any significance.



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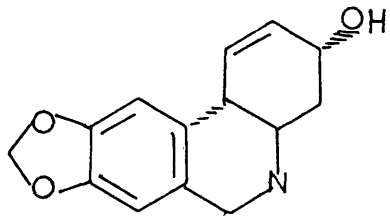

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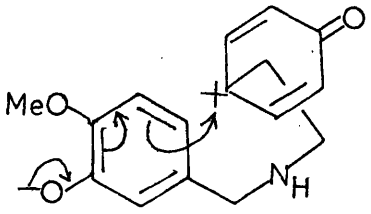

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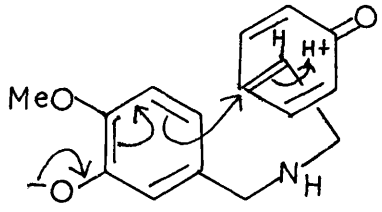

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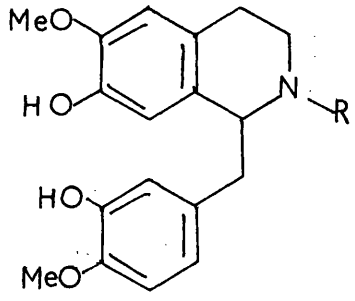

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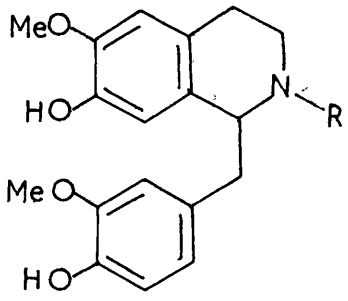

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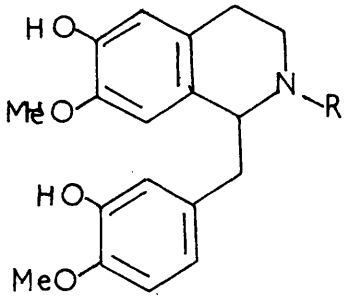

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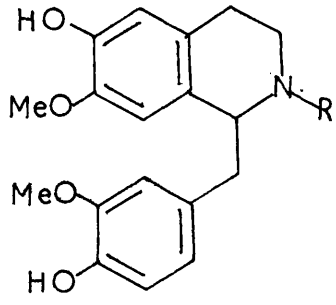
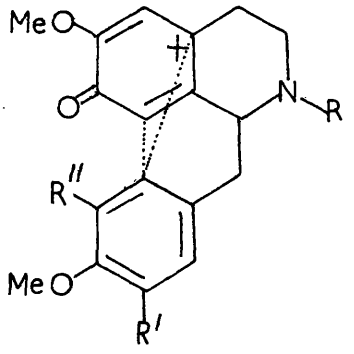


269

In addition to the reported reaction of α-hydroxy-reticuline (226; R=H), one other investigation has been reported of a benzylic alcohol as precursor to an isoquinoline. The amine, β-hydroxy-O-methylbelladine (259) has been synthesized[137] and undergoes facile ring closure to cherylline (261) under acidic or basic conditions. The reactive species was apparently the quinone methide (260). This warrants comparison with norbelladine (262), regarded as the biosynthetic precursor of the crinine-type of alkaloids, and related compounds. For this class of alkaloids, eg. crinine (263), instead of aryl - benzyl coupling, as in (260), aryl - aryl coupling is required, such as represented in (264). Thus the difference between the structures of cherylline (261) and crinine (263) may be compared with the differences between morphinanedione and isopavine alkaloids. It is interesting to note that if aryl annelation[103,104] of O-methylnorbelladine to oxocrinine (185) occurs through the quinone methide (265), then, assuming an antiperiplanar process the C_{11}-H_R hydrogen is obtained from the reaction medium. Thus if this mechanism were operating, whether C_{11}-H_S in (185) is in the same or the opposite configuration as in norbelladine would depend on the course of elimination of hydrogen during the formation of the quinone methide (265).

Returning to the biosynthetic pathways of 1-benzyliso-quinolines, four O,O-dimethylated derivatives of (nor)-laudanosoline (135) exist, where O-methylations occur in different rings. These are (nor)reticuline (266; R=H or Me), (nor)orientaline (267; R=H or Me), (nor)protosinomenine



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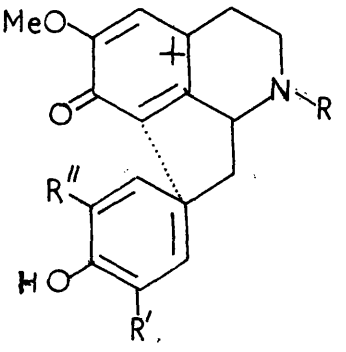

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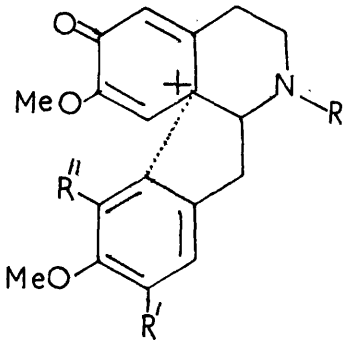

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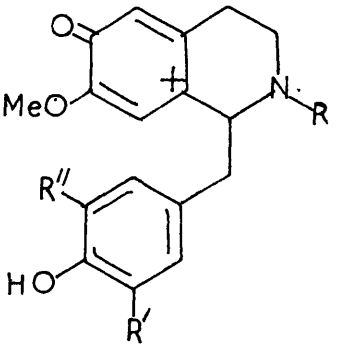

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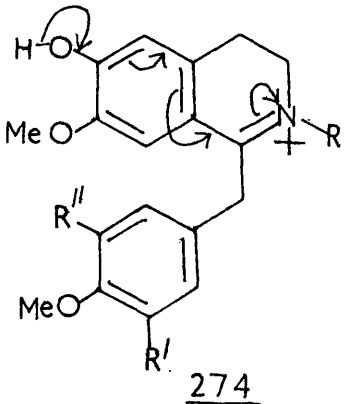

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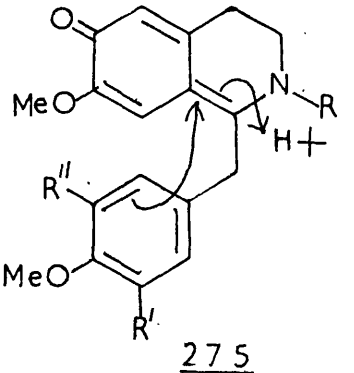

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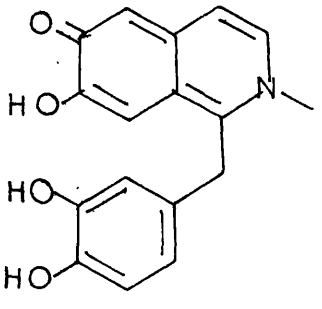

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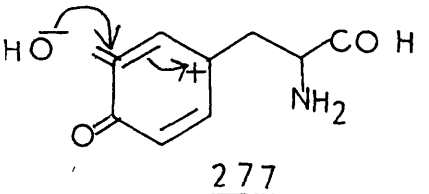

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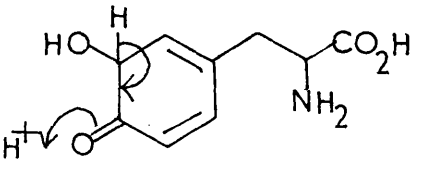

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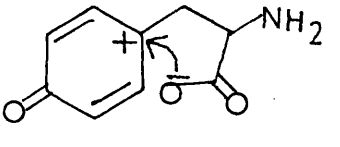

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(268; R=H or Me), and (nor)3',7-O,O-dimethyl laudanosoline (269; R=H or Me). Assuming two-electron oxidation at the isoquinoline nucleus, and occuring at an available phenol, then the appropriate oxidation products would be (270; R=H or Me), (271; R=H or Me), (272; R=H or Me) and (273; R=H or Me) respectively. The potential courses of annelation by "phenolate" attack are then evident, and are shown by the dotted lines. The same annelation possibilities are also evident if the corresponding quinone methides are examined.

Considering each of the four compounds in turn as potential precursors of other isoquinoline alkaloids, on a mechanistic basis only, then:-

1	(nor)reticuline (266)	(270)	fully aromatic 1-benzyl-isoquinolines, aporphines, morphinanes, berbines, 5-hydroxyberbines, pavines, isopavines.
2	(nor)orientaline (267)	(271)	Fully aromatic 1-benzyl-isoquinolines, proaporphines (⟶ aporphines), and, if ring closure *para* to phenolic groups is not biosynthetically essential, pavines, isopavines.

3	(nor)protosinomenine (268)	(272)	aporphines morphinanes berbines erythrina alkaloids.
4	3',7-O,O-dimethyl laudanosoline (269)	(273)	no annelations.

Evidence against some potential conversions has been obtained by means of labelling studies. Thus it has been shown that protosinomenine (268; R=Me) was not incorporated into morphine[138] in Papaver somniferum, or into sinomenine[139] in Sinomenium acutum, or into berberine[140] in Hydrastis canadensis. An apparent success of the above scheme though, is the immediate choice of (nor)protosinomenine (268) as a precursor to aporphines when (nor)reticuline (266) and (nor)orientaline (267) have been shown to be ineffective as biosynthetic precursors, such as to some aporphines of Dicentra eximia in the extensive investigations[130] by Battersby et al. An alternative intermediate, the 1,2-dehydro-derivative (274) of protosinomenine (268; R=Me) should also be considered. The anhydro-base (275) of (274) is a quinone methide and annelation could conceivably occur as shown in (275). Such anhydro-bases are not without precedent.[141,142] Thus anhydro-N-methylpapaveroline (276) was obtained[142] in quantitative yield on treatment of the corresponding hydrochloride salt with pyridine, and various anhydro-bases of flavylium salts are known.[143]

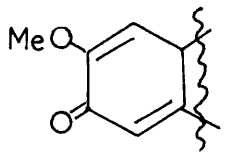
If the same oxidative process, as suggested for the annelations of 1-benzylisoquinolines by carbonium ions, is

applied to tyrosine, then a similar carbonium ion (277) may be generated,[144] and addition of hydroxide ion β to the carbonium ion would then generate dopa through (278). An alternative reaction sequence for (277) is that involving attack by carboxylate, as in (279), thus leading to dopachrome, 6-hydroxydopamine, and for production of melanins.[145,146,147]

If a monomethyl ether of a 4,5-dialkyl-1,2-diphenol is further oxidized and hydroxylated by an ionic process, eg. (280), then a 1,2-dialkyl-3,4-dihydroxy-5-methoxybenzene, eg. (281), would be produced. If this is extrapolated to 1-benzylisoquinolines and related compounds of type (282), oxidation would then give the carbonium ion (283), with hydroxylation at C-10, or at C-8 (284). Possible examples of this are capaurimine (285; R=H) and capaurine (285; R=Me). Similarly, oxidation of "6-hydroxy-7-methoxy" compounds would give "5,6-dihydroxy-7-methoxy" compounds (286). This is an unknown oxygenation pattern for ring D of berbines and this is consistent with this class of alkaloids being derived only from reticuline. The oxygenation pattern is, however, exemplified by thalifendlerine (287) and hernandine (288).

Anomalous oxydation patterns

A more searching test of a predictive method is the application to apparently anomalous products. One of the simplest compounds of the 1-benzylisoquinoline alkaloids is an aromatic example, takatonine (289). Applying the ionic mechanism, in order to aromatize the pyridine ring a phenolic



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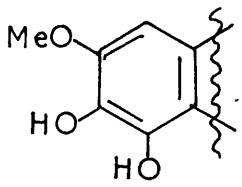

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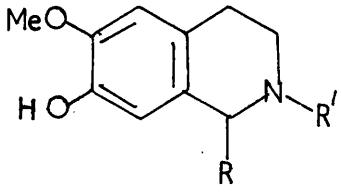

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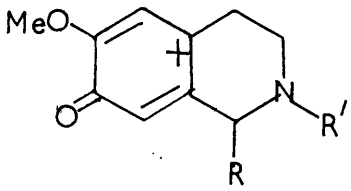

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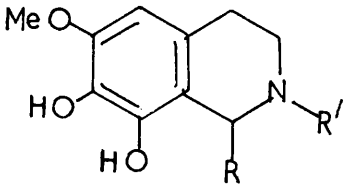

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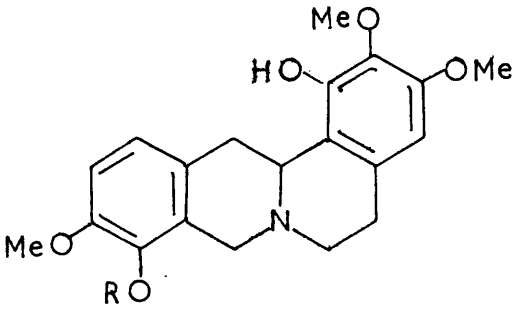

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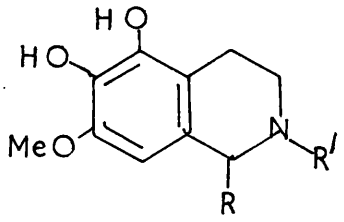

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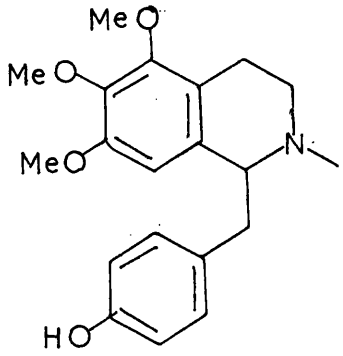

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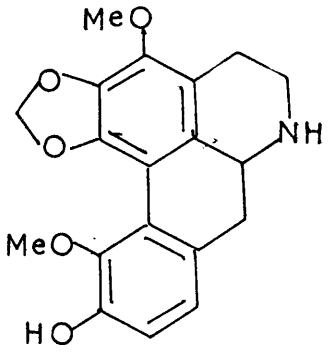

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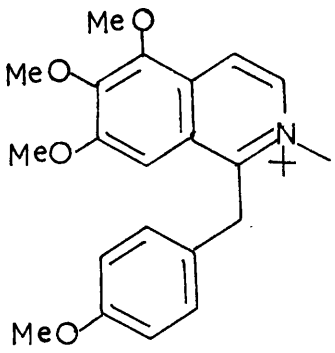

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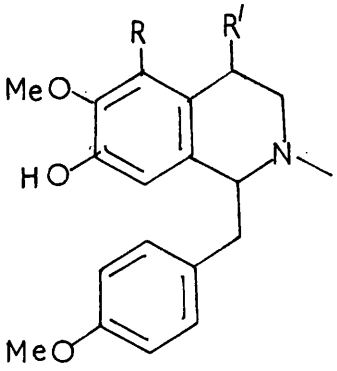

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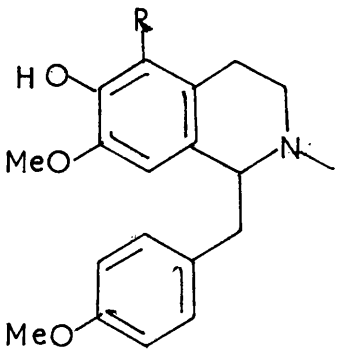
group is required at C-7, so the presumed precursor of takatonine would be (290; R=H or OMe, R^1=H), being oxidized to the 4-hydroxy analogue. But if (290; R=H, R^1=OH) were the precursor, then methylation and demethylation would be required to generate a phenolic group at C-6, and hence hydroxylation at C-5, all this occuring with a compound bearing a benzylic hydroxyl group or on the corresponding aromatic compound. Alternatively, oxidation of the 6-hydroxy-7-methoxy compound (291; R=H) could give the 5-oxygenated derivative (291; R=OH or OMe), with subsequent methylation and demethylation to (292; R=H), a 7-hydroxy compound, oxidation of which could then afford takatonine (289).

Although crotonosine (294) does not seem at first to fit the required pattern, it has been shown[148,149] that (+) coclaurine (293) was an efficient precursor of (+) crotonosine (294), whereas (+) isococlaurine (295) was not incorporated in (294) in tracer studies. The obvious intermediate is norglaziovine (296; R=H), with subsequent methylation - demethylation to afford crotonosine (294). Similarly, homolinearsine (297) would be expected to derive from (-) glaziovine (296; R=Me) or (-) norglaziovine (296; R=H).

Presumably the hitherto accepted diradical process for the annelations of 1-benzylisoquinolines would require two separate one-electron oxidations at different sites on a molecule. It is difficult to envisage such oxidations occuring from two different haeme units in one enzyme because of steric problems, the simple haeme units being much bigger than an isoquinoline. Alternatively, two separate oxidations from one



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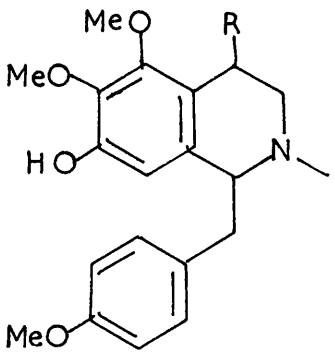

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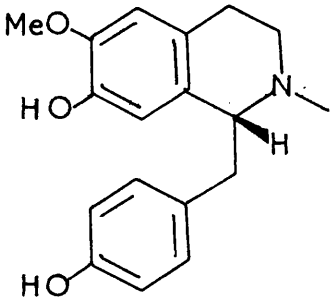

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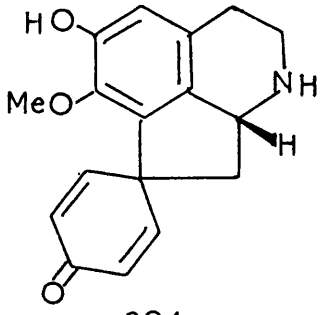

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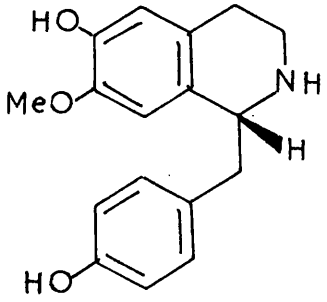

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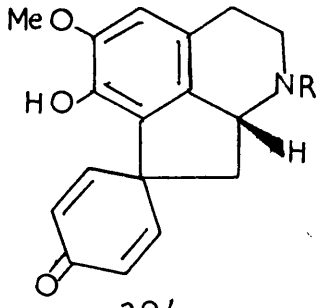

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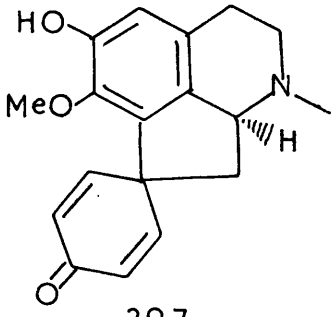

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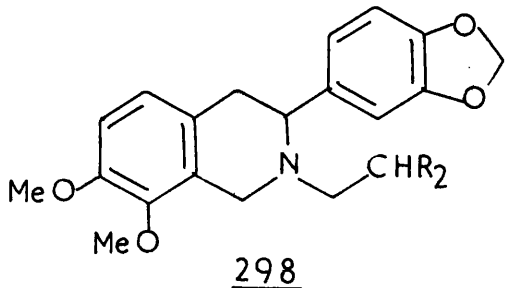
haeme unit by movement of the 1-benzylisoquinoline radical to bring the second site into position could be postulated. More simply, the annelations could be effected by a two-electron oxidation where the site of annelation is controlled by the forced conformation of the 1-benzylisoquinoline, due to the cavity size and shape above the oxidizing site. Hence many dramatically differing enzymes would not be required to produce the wide range of alkaloids found. One principal type, with variations in cavity access by virtue of variations in the haeme sheath, or in position on a cell wall, could well give the observed variety of products. If binding to a cell wall, or other external control, plays a significant part in control of type of product of oxidation, this might prove susceptible to investigation by isolation of enzymes under "vigorous" conditions, to destroy such attachments. By such means extracts from a plant, giving normally a restricted range of alkaloids, might give a wider range of alkaloids.

Conclusions

Using a formal two-electron oxidation of isoquinolines, a predictive technique has been derived which appears capable of assigning the course or courses of oxidations of 1-benzyl-isoquinolines and related compounds on the basis of the methylation pattern.

DISCUSSION

The key intermediate to a synthesis of berberastine was considered to be the 3-arylisoquinoline (298; R + R=O or R=OMe).



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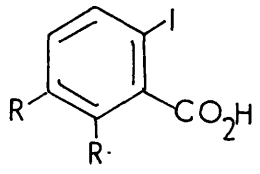
Three routes to such a compound were investigated with varying degrees of success.

The Isocoumarin route

This investigation was designed to parallel one of the earlier successful syntheses[31] of 5-hydroxyberbines by Dyke, Hardy et al, as outlined in Scheme (IX) (R=H). Firstly though, the known[150,151] 2,3-dimethoxy-6-iodobenzoic acid (299; R=OMe) was required. This compound had hitherto been obtained by condensation of 2,3-dimethoxybenzoic acid (306) with formaldehyde to obtain[152] 6,7-dimethoxyphthalide (307), subsequent oxidation to 3,4-dimethoxyphthalic acid (308) and reaction with ammonia[153] to give 3,4-dimethoxyphthalimide (309). Hoffman degradation[154] to 2,3-dimethoxy-6-aminobenzoic acid, with subsequent diazotization and Sandmeyer iodination then was reported[150,151] to give the desired 2,3-dimethoxy-6-iodobenzoic acid (299; R=OMe), this taking five stages from 2,3-dimethoxybenzoic acid. A considerable improvement was obtained by application of the method of Taylor and



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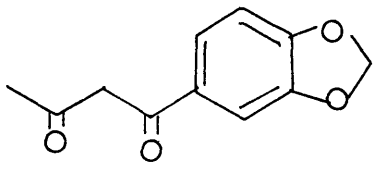

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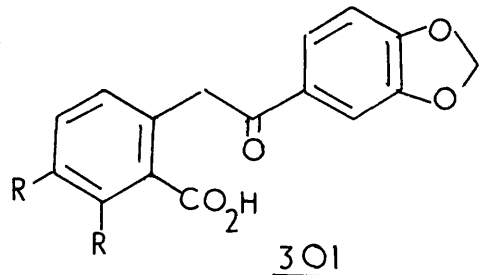

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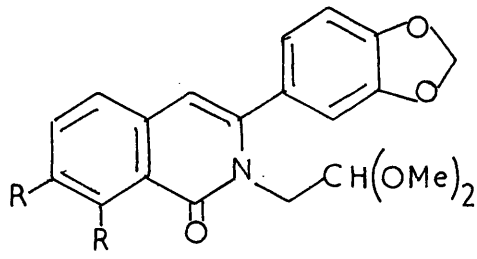

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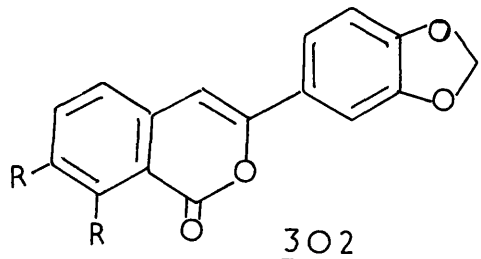

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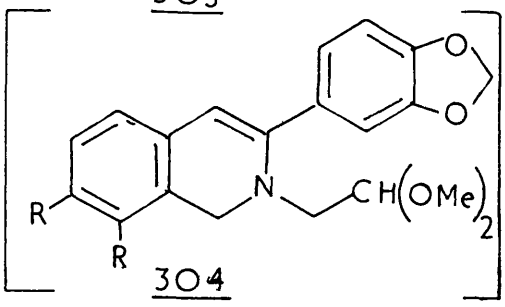

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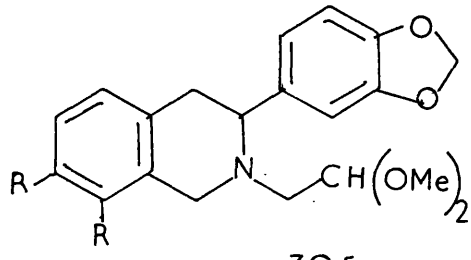

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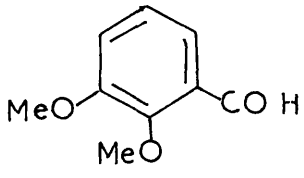
IX



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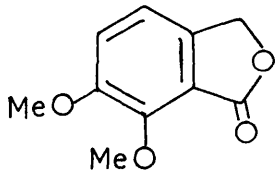

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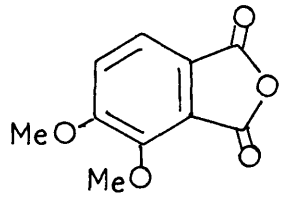

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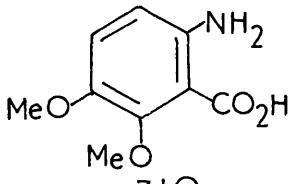

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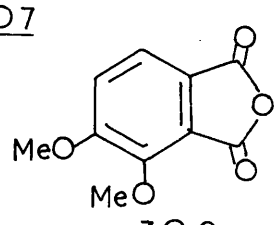

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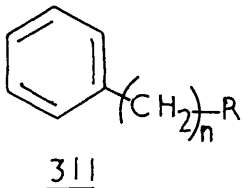

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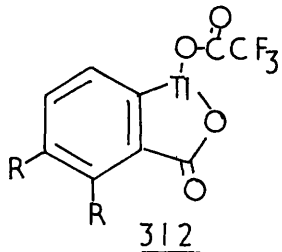

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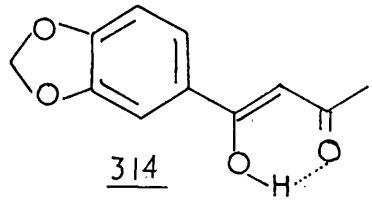

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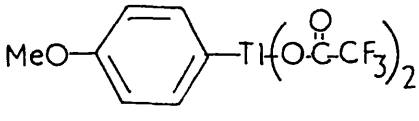

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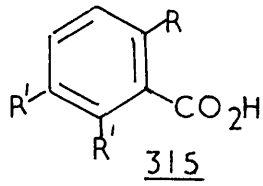


315

McKillop[155,156,157,158] for ortho-iodination of benzoic acid using thallium (III) trifluoroacetate (TTFA). Reaction of benzoic acid with TTFA in trifluoroacetic acid under reflux and subsequent reaction of the apparently uncharacterized organothallium intermediate with aqueous potassium iodide was reported[155,156] to give 2-iodobenzoic acid (299; R=H) in excellent yield. This type of reaction of TTFA with a variety of substrates and subsequent iodination has been investigated[157,158] to determine some of the features required for orientation control. In the series of carboxylic acids (311; n=0, 1, 2, 3; R=CO_2H), or esters (311; n=0, 1, 2; R=CO_2Me), it was found that ortho-iodination only predominated if n=0 or 1. Similarly, for the series of alcohols (311; n=1, 2, 3; R=OH) or methyl ethers (311; n=0, 1, 2; R=OMe) it was found that ortho-iodination predominated only for n=1 or 2. This is consistent with a 5- or 6-membered cyclic complex being essential for ortho-reaction, and, for a benzoic acid, a structure such as (312) was envisaged.

Thallylation of 2,3-dimethoxybenzoic acid was effected by heating with TTFA in trifluoroacetic acid for five hours under reflux, with subsequent recovery of the solvent. Due to problems of solubility a PMR spectrum of the uncharacterized organothallium intermediate could only be obtained using trifluoroacetic acid as solvent. The spectrum was not successfully interpreted because a signal was suspected of being masked by the strong solvent signals at ca. 11 p.p.m.

It was obvious, though, that the large ortho couplings[159] (ca. 1025 Hz), observed for 4-methoxyphenylthallium (III) bis-trifluoroacetate[155] (313) were not present. The lowest-field signal was observed at about 11 p.p.m., whereas for a coupling constant Tl to H of about 1000 Hz, and an assumed base position of about 7 p.p.m. or 420 Hz, the lowest-field signal would be at about 920 Hz, or 15.3 p.p.m. This large discrepancy would lend support to, but not prove, the structure of the organo-thallium intermediate to be (312; R=OMe). Reaction of the intermediate with aqueous potassium iodide gave the 6-iodoacid (299; R=OMe) in 83% yield from 2,3-dimethoxybenzoic acid.

The TTFA salt was prepared from thallium (III) oxide and trifluoroacetic acid and the thallium (III) oxide was derived from several different batches of varying quality. It was found necessary to check the quality of different preparations of TTFA in trifluoracetic acid by small scale preparations of the 6-iodobenzoic acid (299; R=OCH_3) and to increase the TTFA/substrate ratio according to the conversion obtained. From such trials, mixtures of 2,3-dimethoxybenzoic acid and the desired 6-iodobenzoic acid (299; R=OMe) were obtained. Separation was readily effected by subjecting the mixture to Fischer esterification with methanolic hydrogen chloride. The starting material was obtained as the methyl ester whereas the 6-iodo acid (299; R=OMe) was not esterified and the separation was near quantitative. Esterification of (299; R=OMe) was readily accomplished with diazomethane.

Methylenation of catechol was accomplished by essentially a known procedure,[160] with minor modification to avoid the need for special equipment. Acetylation of the resultant methylenedioxybenzene with acetic anhydride and perchloric acid gave[161] 4-acetyl-1,2-methylenedioxybenzene in good yield, and conversion to 1-(3,4-methylenedioxyphenyl)butan-1,3-dione (300) was accomplished by repetition of a known method.[162,163] From the PMR spectrum of the β-diketone (300) it was concluded that, in deuterochloroform solution, the compound (300) was ca. 85% enolic (314).

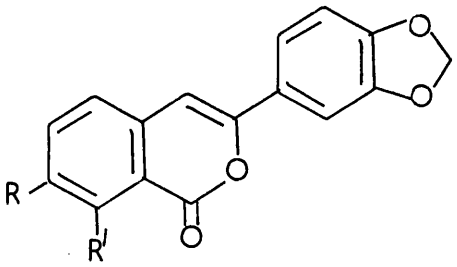
Attempts to arylate the β-diketone (300), with the 6-iodo acid (299; R=OMe) using alcoholic sodium alkoxides and various metallic copper catalysts were unsuccessful, in contrast to the successful investigations reported[31,164] for analogous reactions using 6-iodobenzoic acid. The crude reaction products were investigated by means of their PMR spectra. From these it was concluded that the main product (ca. 70% yield) was a 6-alkoxybenzoic acid (315; R=OMe or OEt, R^1=OMe) where methanol or ethanol were used. For (315; R=OEt, R^1=OMe) a triplet at 1.31 p.p.m. (J=7 Hz) and a quartet at 3.98 p.p.m. (J=7 Hz) were evident. That such a reaction occured was not too suprising in view of, for example, the known reaction of (299; R=OMe) with the sodium salt of benzyl alcohol to give[150,151] (315; R=$OCH_2C_6H_5$).

Repetition of the previously reported reaction[31] of 2-iodobenzoic acid with the -diketone (300) was then undertaken and the major product was found to be 2-ethoxybenzoic acid[165] (315; R=OEt, R^1=H). The expected isocoumarin (302; R=OCH_3)

was also obtained, but in slightly lower yield than previously reported. The PMR spectrum of 2-ethoxybenzoic acid (315; R=OEt, R^1=H) exhibited signals at 1.43 p.p.m. (triplet, J = 7 Hz) and 4.16 p.p.m. (quartet, J = 7 Hz). When potassium t-butoxide and t-butanol were used, it appeared that the 6-t-butoxy acids (315; R=H, R_1= O-t-Bu) (9% molar) and (315; R=OCH_3, R_1=O-t-Bu) (25%) were formed since sharp singlet PMR signals were observed at 1.32 p.p.m. and 1.31 p.p.m. respectively. Only in the case of the reaction involving sodium ethoxide and 2-iodobenzoic acid, was the major acidic product isolated and characterized, as the known[165] 2-ethoxybenzoic acid.

The arylation of the β-diketone (300) with (299; R=OCH_3) was successfully carried out using sodium hydride in dimethylformamide[166,167] at reflux temperature. However, the product was not the anticipated isocoumarin (302; R=OMe). In the PMR spectrum of the product, only one methoxyl group was evident, and, from the mass spectrum, the molecular weight was apparently 312. The product was either the 8-hydroxyisocoumarin (316; R=OMe, R^1=OH) or the 7-hydroxyisocoumarin (316; R=OH, R^1=OMe). Although the product exhibited no obvious phenolic characteristics, thus was insoluble in aqueous bases and did not give a positive test with ferric chloride, this could well have been due to the generally low solubility of the compound. Purification was accomplished by either liberal washing with polar organic solvents, or by vacuum sublimation. Methylation with iodomethane and potassium carbonate in dimethylformamide gave the required

isocoumarin (302; R=OMe) in near quantitative yield, whose molecular weight was, by mass spectrometry, 326.



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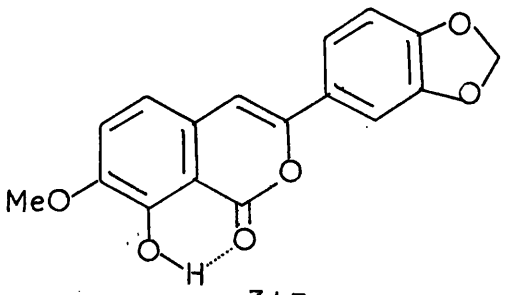

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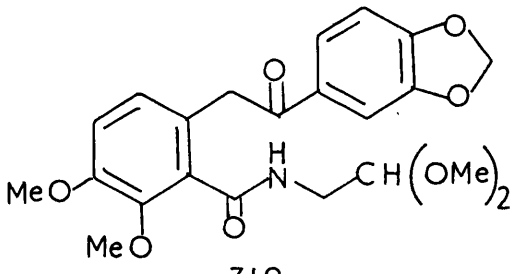
In the infrared (IR) spectrum of (302; R=OMe), (316; $R=R^1$=OMe), absorption at 1725 $cm.^{-1}$ was observed, whereas absorption was found at 1670 $cm.^{-1}$ in the demethylated material. Since these absorptions were attributed to the carbonyl group, and a large difference between the two compounds was evident, the frequency drop was considered due to intramolecular hydrogen bonding (317) and the demethylated material was therefore the 8-hydroxyisocoumarin (316; R=OMe; R^1=OH). Berberrubine (318; R=H), a 9-hydroxyberbine derivative, obtained by either treatment of oxyberberine (318; R=Me) with hot acids,[168] or by hydration and thermolysis of berberine,[169] is an example of a product derived from demethylation of an ether ortho to a carbonyl group.

The 7,8-dimethoxyisocoumarin (302; R=OMe) was more readily obtained by treating the cooled arylation mixture, containing the demethylated compound (317), with iodomethane and potassium carbonate.

Attempts to prepare the isocarbostyril (303; R=OMe) reaction of aminoacetal with the isocoumarin (302; R=OMe)

were unsuccessful. Both isocoumarins (302; R=OMe) and (317) were only slightly soluble in alcohols so a simple preparative analogy with earlier investigations[31] was not possible. Reactions carried out in either neat aminoacetal or aminoacetal in DMF at reflux temperature, gave intractable mixtures, as did similar reactions in hot dimethylsulphoxide (DMSO) or hexamethylphosphortriamide (HMPT). Stirring a suspension of the isocoumarin (302; R=OMe) with aminoacetal in HMPT or DMSO for two weeks at ambient temperature gave the amide (319). In the PMR spectrum of (319),

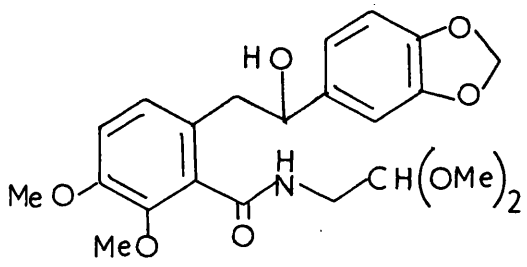


319

couplings of the $\left[NHC\underline{H}_2CH(OMe)_2\right]$ methylene protons with both the $\left[-NH-\right]$ proton and the methine proton were observed ($J = 5.5$ Hz). In the IR spectrum of (319), the broad absorption (1650-1690 $cm.^{-1}$) in the carbonyl range did not permit a clear interpretation, but the absorption at 3390 $cm.^{-1}$ was ascribed to the amidic hydrogen.

Attempts were made to cyclize the keto-amide (319) to the desired isocarbostyril (303; R=OMe), but without success.

From the Hauser reaction,[7,8,9,10,170] ortho lithiation of secondary amides and subsequent condensation with electrophiles, various hydroxy-amides have been reported, and cyclizations to afford 3,4-dihydroisocarbostyrils have been claimed,[7,8] though, as discussed earlier, such claims must be treated with reservation due to the subsequent investigations by Bailey and DeGrazia.[9,10] Despite this confusion, since a ketone had only to be reduced to an alcohol to provide a similar intermediate to those used[7,8,9,10] for cyclizations, this method of cyclization was investigated.



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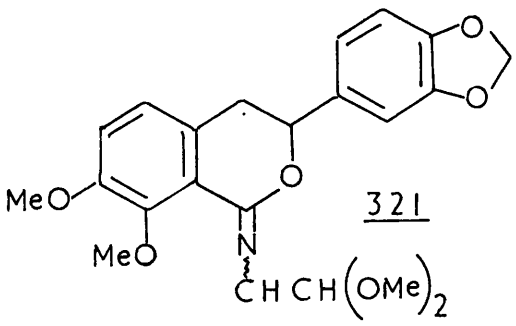
Reduction of the keto-amide (319) to the hydroxy-amide (320) was readily accomplished with aqueous ethanolic sodium borohydride. In the PMR spectrum of the hydroxy-amide (320), the signal for the [-NH-] proton was again observed as a broad "triplet" (6.63 p.p.m., J= 5 Hz). The [C-H(OH)] methine proton [4.74 p.p.m., "triplet", J= 6-7 Hz] and [Ar-CH_2-] methylene protons [2.9 p.p.m., "doublet", J= 6-7 Hz] were observed as broad signals, sharpening somewhat after deuteration. The [-CONHCH_2-] methylene protons were observed as a multiplet, centred at about 3.6 p.p.m., in

contrast to the apparent triplet and presumed doublet of doublets in the preceeding keto-amide (319). The multiplicity was presumably due to non-equivalence of the [-CONHC$\underline{H}_2$-] methylene protons, thus an ABXY system was presumed for the [-CONHCH$_2$C$\underline{H}$<] protons. No attempt was made to unravel this complex system in terms of coupling constants.

On deuteration, the appearance of the spectrum reflected the two stages involved, with sharpening of the signals at the initial deuteration of the alcohol and an increase in the apparent complexity of the signals due to the methine protons. The latter was partly due to the removal of the broad signal in the same region due to the [-OH] proton. After prolonged deuteration, with major loss of signals due to the [-NH-] proton, the overall pattern of the signals due to the [CONH-C$\underline{H}_2$-] methylene protons changed, but was still complex due to an ABX system.

Cyclization of the hydroxy-amide (320) with weak acids was attempted. Reaction with hot 90% acetic acid was monitored by inspection of the IR spectra of dried aliquots, and increasing reaction time gave an increasingly strong absorption at 1720 cm.$^{-1}$, with a concomitant diminution in amidic absorption at 1645 cm.$^{-1}$. It was therefore assumed, but not proven, that the imino-isocoumarin (321) was formed,



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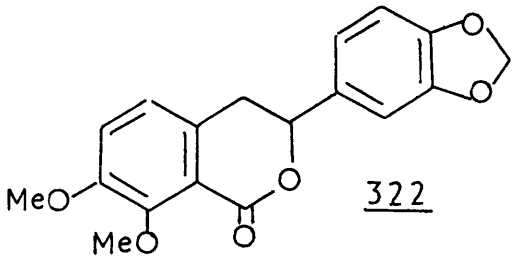
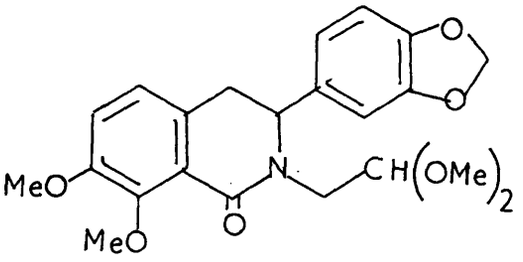


322

with subsequent hydrolysis to the 3,4-dihydroisocoumarin (322). Use of strong acids such as anhydrous sulphuric or trifluoroacetic acids, gave intractable multicomponent mixtures (by TLC), presumably due to additional reactions of the acetal group.

Reaction of (320) in acetic acid - methanol solution was investigated, the methanol being optimistically added as a diluent and to enable colder reaction conditions to be investigated. Very little change appeared to occur in cold reactions but, at reflux temperature, one major product was obtained, the IR spectrum of which exhibited absorptions at 3320 $cm.^{-1}$ and 1660 $cm.^{-1}$ (broad). Hopes that the desired product, the 3,4-dihydroisocarbostyril (323), had been obtained, and that the absorption at 3320 $cm.^{-1}$ was merely due to methanol solvate, were rapidly dashed on examination of the PMR spectrum of the product. For methanol, in deuterochloroform solution, the methyl protons give a signal at 3.48 p.p.m. whereas the additional 'methyl' signal was observed at 3.13 p.p.m. In the mass spectrum of the product m/e 447 was evident, and in the crude product, a weak m/e 476 was also found. The structure of the product was therefore the methoxy-amide (324; R=Me) and m/e 476 corresponded to the acetoxy-amide (324; R=Ac). The methoxy-amide (324; R=Me) was presumably formed through the carbonium ion (325). It appeared that the intermediate carbonium ion (325) was more readily trapped by methanol[171] than by an intramolecular cyclization involving the amide



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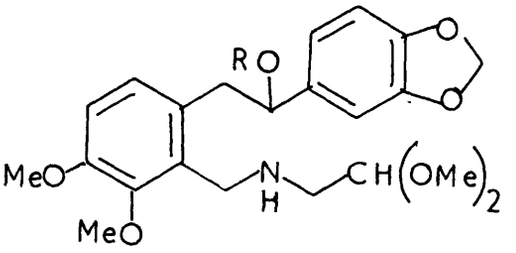

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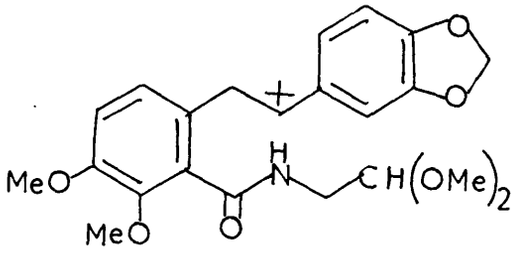

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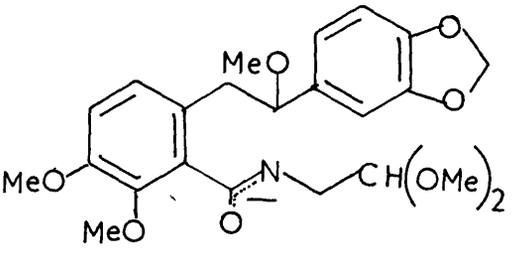

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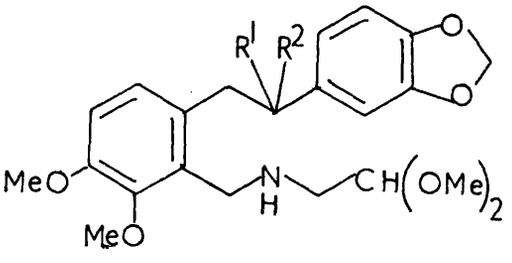

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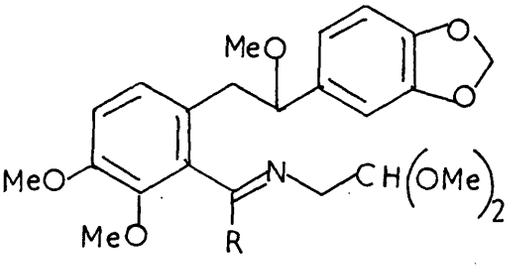


328

group. In addition, the oxygen of the amide group was a better nucleophile than the nitrogen atom. This was similar to the results of alkylation of secondary amides[11].

The methoxy-amide (324; R=Me) could not be cyclized under a variety of conditions and was thermally stable to over 200°. When (324; R=Me) was treated with sodium hydride in DMF, effervescence was observed, and presumably the amide anion (326) was formed but, after heating at reflux temperature, only (324; R=Me) was recovered.

General comments on the complexity of the PMR spectra of the hydroxy-amide (322) were also applicable to the methoxy-amide (324; R=Me).

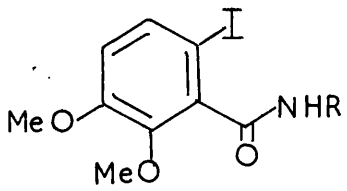
Reduction of the amide function in the keto-amide (319), or in the hydroxy- or methoxy-amides (324; R=H or Me) seemed to be the next step required, thus eliminating the competitive carbonyl nucleophile. It was then hoped to investigate cyclization of either the keto-amine (327; $R_1 + R_2 = O$), the hydroxy-amine ($R_1 = H$; $R_2 = OH$), or the methoxy-amine ($R_1 = H$, $R_2 = OMe$). For convenience, reduction of the methoxy-amide (324; R=Me) with lithium aluminium hydride was first investigated but without success even when using lithium aluminium hydride in dioxan at reflux temperature. A small amount of basic material was obtained by using diborane in diglyme[172] but this product mixture proved intractable. Similar results were obtained when reductions were attempted on the hydroxy-amide (324; R=H). With prolonged and vigorous reducing conditions greater amounts of basic material were obtained, but examination of the crude

products by PMR revealed an absence of signals around 3.3 p.p.m., hence the acetal group was essentially lacking[173] in the product mixture.

Both imidates[174,175] and imidoyl halides[176,177,178] may readily be reduced to the corresponding amines. Accordingly the methoxy-amide (324; R=Me) was treated with phosphorus pentachloride in pyridine[178] and attempts were made to obtain the desired imidoyl halide (328; R=Cl) by cold extraction procedures but only crude starting material (324; R=Me) was obtained. In case very facile hydrolysis of the imidoyl halide (328; R=Cl) were occuring, reduction with sodium borohydride was carried out on the crude reaction mixture, but again only starting material (324; R=Me) was obtained. Phosphorus pentachloride was substituted by thionyl chloride, but with no improvement. Alcoholysis of the crude reaction mixtures was also investigated,[178] but again only crude starting material was recovered and there was no evidence that the imidoyl halide (328; R=Cl) was formed.

The methoxy-amide (324; R=Me) reacted readily with triethyloxonium tetrafluoroborate,[179,180] and the uncharacterized intermediate was reduced <u>in situ</u> with sodium borohydride, resulting in a complex mixture of bases (TLC). Investigation of the mixture by PMR confirmed the complexity of products, and the spectra were notable by the absence of signals attributable to the methylenedioxy and acetal groups. Although the conditions for the reaction of triethyloxonium tetrafluoroborate were varied, the nature of the complex mixture of bases could not be improved.

Prior to encountering the problems of reducing the amide group, alternative methods of introducing the aminoacetal group were considered. One possibility seemed to be the use of a 6-iodobenzamide [329; R=H or $-CH_2CH(OMe)_2$] instead of 2,3-dimethoxy-6-iodobenzoic acid (299; R=OMe) in reaction with 3,4-methylenedioxyphenylbutan-2,4-dione (300).



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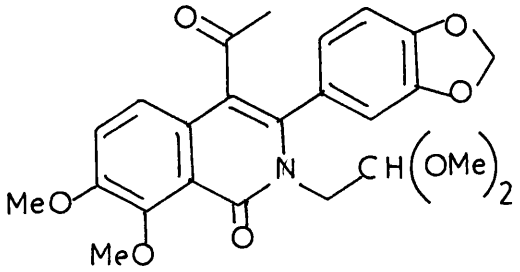
Accordingly, both amides were prepared by treatment of 2,3-dimethoxy-6-iodobenzoic acid (299; R=OMe) with thionyl chloride to obtain the corresponding uncharacterized acyl halide, further treatment of which with either aqueous ammonia or with aminoacetal in benzene gave (329; R=H) or [320; $R=CH_2CH(OMe)_2$] respectively.

One trial condensation of the amide-acetal [329; $R=CH_2CH(OMe)_2$] with the β-diketone was undertaken, using the same reaction conditions as for the preparation of the isocoumarin (317). A product was obtained in small yield whose IR spectrum exhibited absorptions at 1660 $cm.^{-1}$ and 1720 $cm.^{-1}$. The product was found (by TLC) to be contaminated with a little starting material but not with 3,4-methylenedioxyacetophenone, whose carbonyl absorption was found at 1675 $cm.^{-1}$. The product appeared to contain a ketone, unlikely to be adjacent to the 3,4-methylenedioxy-

phenyl group, and an amidic group. The probable structure of the product was considered to be (330). The carbonyl group



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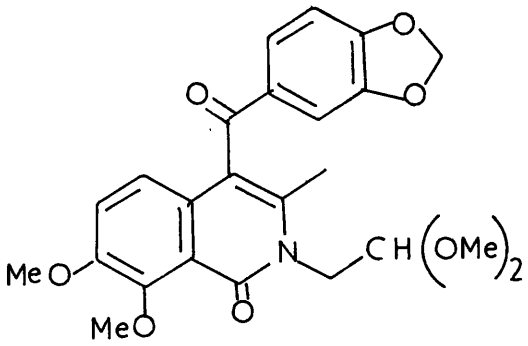
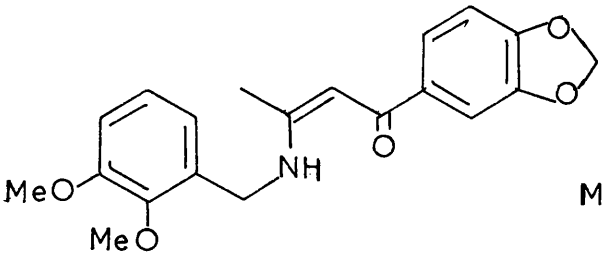


331

in 4-benzoylisocarbostyrils has been found[181,182] to be well below 1700 cm.$^{-1}$, and in an analogous 3-aryl-4-ethoxalylisocarbostyril the absorption due to the ketone group was[182] at 1666 cm.$^{-1}$ hence structure (331) seemed unlikely. Regrettably this reaction was not investigated further since all work on this route was abandoned.

Condensation of 2,3-dimethoxybenzylamine with the β-diketone (300) gave the vinologous amide (332). The PMR spectrum of (332) closely resembled that of 3,4-methylenedioxyacetophenone in the aromatic region, with, of course the additional signals due to the benzylamino group. Anomalous attack at the ketonic group at C-1 would give compound (333; R=H) and little deshielding of the 3,4-methylenedioxyphenyl group would be expected. Compounds of type (332) were predictable in view of earlier examples of such condensations. It has been suggested[183] that the reaction



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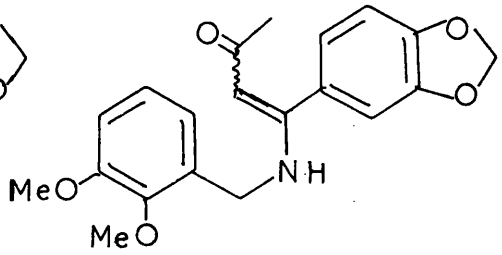

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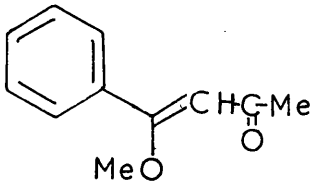

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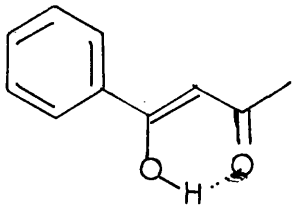

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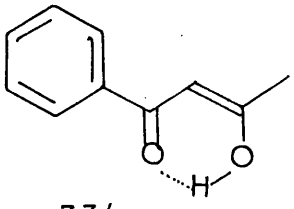

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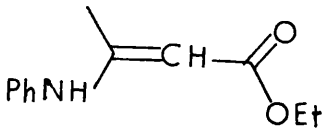

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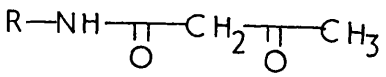

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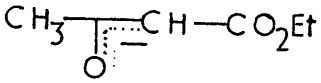

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course is by 1,4- or β -addition to the enolic form of a -diketone[184] but this is inconsistent with, for example, the observations of Weygland.[185] Treatment of benzoylacetone with either methyl orthoformate or diazomethane, or treatment of the sodium salt of benzoylacetone with dimethyl sulphate, all afforded the same product, 4-methoxy-4-phenylbut-3-en-2-one (334). Thus the enolic form is (335) rather than (336). If such 'β-addition' of an amine were to occur then the product would be, for example, (333), whereas compounds of type (332) are obtained. Although condensations of amines with 2-bromo-3-ethoxy-3,4-diphenylpropenone have been reported, with the appearance of a reaction course by β-addition, such products could equally well arise by condensation at the carbonyl group.

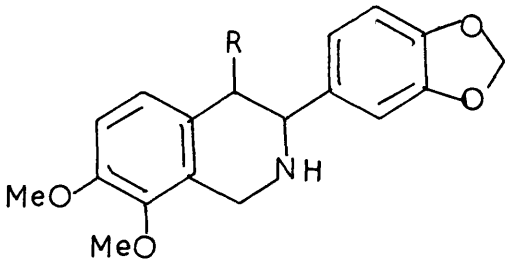
The course of reaction of amines with β-keto esters appears unclear when some examples are compared. Thus reaction of aniline with ethyl acetoacetate gave[186,187,188] ethyl 3-anilinocrotonate (337), whereas a range of substituted anilines gave,[189,190] with ethyl acetoacetate, N-acetoacetyl derivatives (338). For (337) though, reaction was carried out with addition of some acetic acid, whereas for (338), pyridine was added. This is consistent with repression of condensation with the ketone by formation of the enolate (339), and reaction at the ester function for reactions in the presence of pyridine. Conversely, repression of enolate salt formation by the addition of a weak acid presumably aided reaction with the ketonic tautomer (340) of acetoacetic ester.

Reaction of benzylamine with acetoacetic ester was carried out in the absence of reagents such as pyridine or acetic acid to afford N-acetoacetyl benzylamine (338; R=$C_6H_5CH_2$-) as the only isolated product.

The aminoacetal route

A convenient and versatile synthesis of isoquinolines involves the acid-promoted cyclizations of benzylamino-acetals,[192,193,194] particularly where the aromatic ring bears activating alkoxy substituents. The resultant 4-hydroxy-1,2,3,4-tetrahydroisoquinolines may then be reduced or oxidized to remove the hydroxyl group, or the hydroxyl function may be displaced by nucleophiles.

The desired compound was the 3-aryl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (341; R=OH), reduction of which to (341; R=H) would then be necessary, and further conversion to berberastine would then parallel previous investigations by Dyke and Hardy.[29,30] The acetal precursor was therefore α-(2,3-dimethoxybenzylamino)-3,4-methylenedioxyphenyl-acetaldehyde dimethylacetal (341). The known unsubstituted analogue (345) has been prepared[194] by condensation of benzylamine (342) with glyoxal monoacetal (343), and reaction of phenylmagnesium bromide with the imine (344) to obtain (345). In order to extrapolate the reaction sequence (342) to (345) to obtain the desired aminoacetal (341), two known compounds, 2,3-dimethoxybenzylamine[195] and 3,4-methylenedioxy-phenylmagnesium bromide,[196] would be required. Other investigators, though, have found[197] the reported syntheses[198,199]



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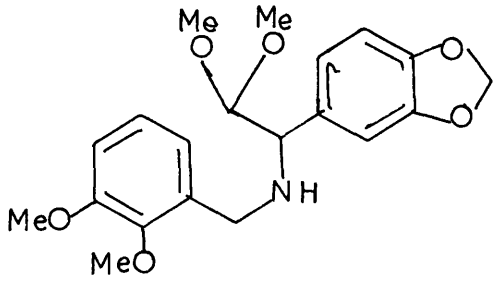

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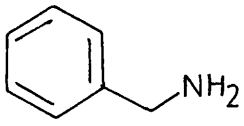

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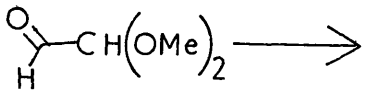

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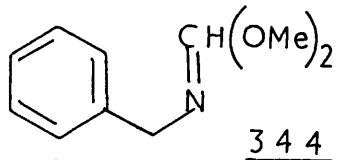

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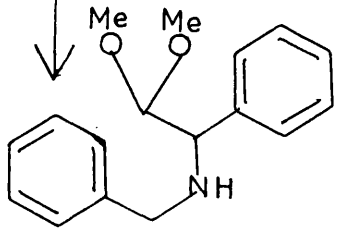

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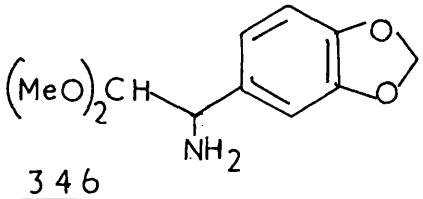

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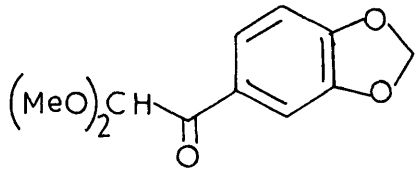

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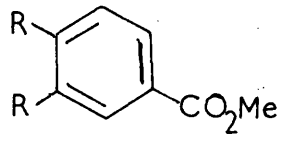

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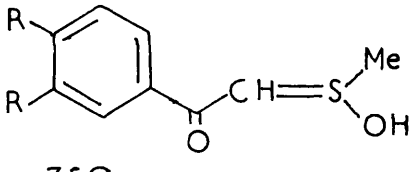

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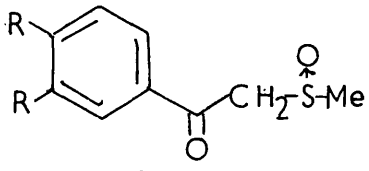

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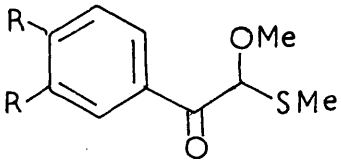

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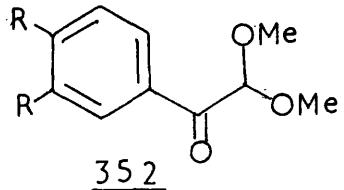

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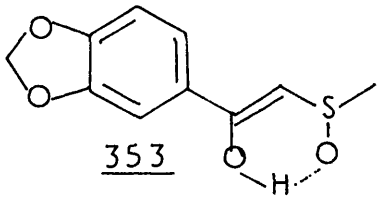

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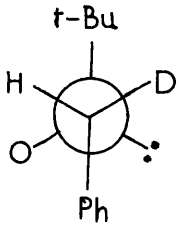
of glyoxal monoacetal difficult to reproduce and yields, if any, were absymal. Preliminary investigations confirmed the difficulties and an alternative synthesis of (341) was sought.

Two possible synthetic approaches to (341) may readily be envisaged, condensation of 2,3-dimethoxybenzaldehyde with α-amino-3,4-methylenedioxyphenylacetaldehyde (346) or condensation of 2,3-dimethoxybenzylamine with 3,4-methylenedioxyphenylglyoxal dimethylacetal (347).

Phenylglyoxal acetals are known[199a] and a convenient preparation has been through condensation of benzoate esters (348) with dimethyl sulphoxide in basic solution.[200,201] The resultant β-ketosulphoxide (349; R=H) has been submitted to a Pummerer rearrangement[202] in methanol. The intermediate hemithioacetal may be converted to the acetal, (347; R=H), by trapping methanethiol by oxidation to dimethyldisulphide with iodine. This sequence of reactions was successfully carried out using methyl piperonylate (348; R + R= $-OCH_2O-$). The β-ketosulphoxide (349; R + R= $-OCH_2O-$) was obtained in 84% yield by application of a known procedure.[201] That (349; R + R= $-OCH_2O-$) existed as shown, rather than in the enolic form (353), was evidenced from its IR spectrum, with absorption at 1665 $cm.^{-1}$. In the PMR spectrum of (349; R + R= $-OCH_2O-$), the signals for the $\left[-COCH_2-\right]$ methylene protons were observed as a pair of doublets (4.15 and 4.43 p.p.m., J 14 Hz). Although β-ketosulphoxides do not appear to have been investigated in the PMR sense, the non-equivalence of methylene protons adjacent to a sulphoxide group has been the subject of investigations.

From treatment of (RR/SS) and (RS/SR)-α-deuterobenzyl-t-butylsulphoxide with n-butyllithium, and quenching the anion with water, it was shown[203,204] that the pro-(R)-hydrogen, or deuterium, in the (R)-sulphoxide was more acidic than the Pro-(S)-hydrogen. Thus, if it is assumed that the molecular conformation is as in projection (354), then the carbanion is trans to the oxygen, with maximum separation of charge. Using the argument of maximum charge separation for the carbonyl and sulphoxide groups, the conformation of (349) would then be (358), or the corresponding enantiomer. Thus both hydrogens would be gauche to the sulphoxide oxygen and steric control by chirality of the sulphoxide would not appear to be as strong as in the case of sulphoxides lacking the β-carbonyl group, apart from problems of enolization.

A Pummerer-type rearrangement of (349) was accomplished in 95% yield by heating at reflux temperature in a methanolic iodine solution for at least two hours. With shorter reaction times some evidence for the hemithioacetal intermediate (351; R + R= $-OCH_2O-$) was obtained. In the PMR spectrum of crude (352) obtained from a half-hour reaction, a signal at 2.10 p.p.m. was attributed to the protons on the S-methyl group in (351; R + R= $-OCH_2O-$) (23%). The signal for the methine proton was observed at 5.08 p.p.m. (singlet), so the product had not further rearranged to afford 3,4-methylene-dioxyphenylglyoxal dimethylketal[205] where the "methine" proton would then be aldehydic.



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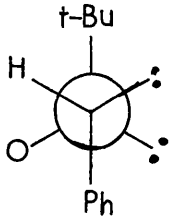

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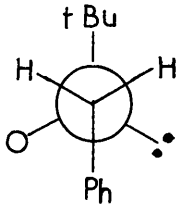

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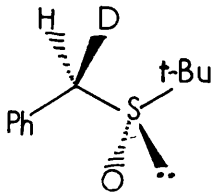

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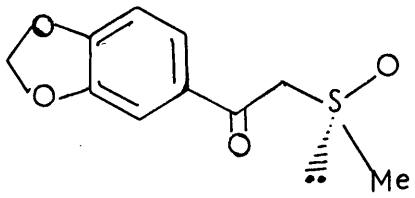

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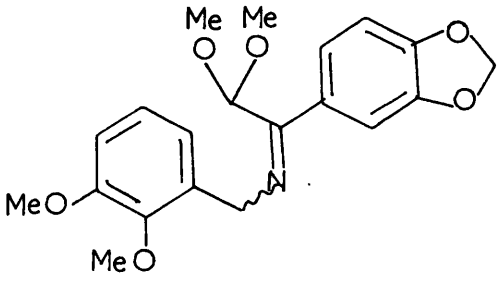

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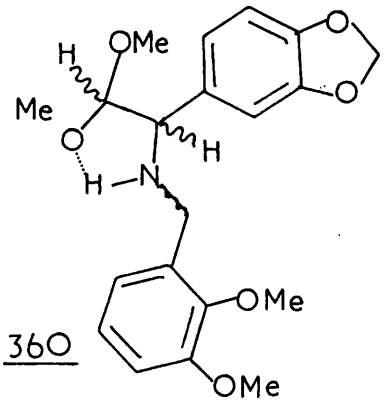

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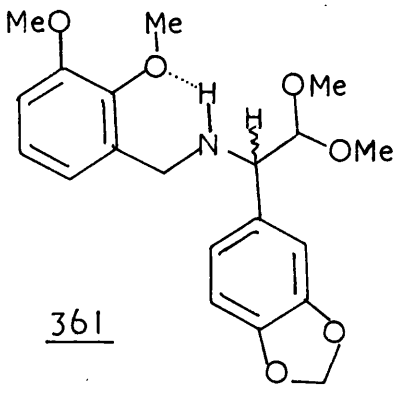

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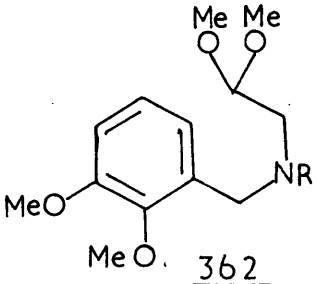

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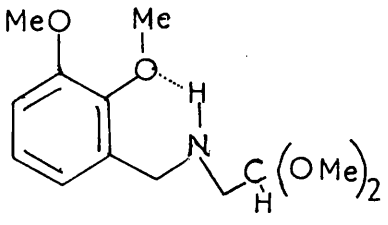

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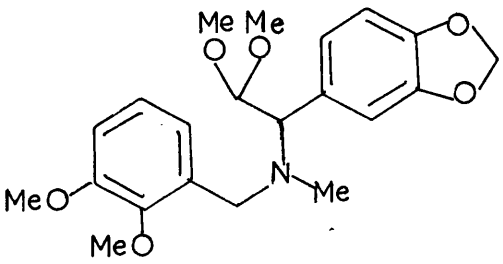

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The oxime of 2,3-dimethoxybenzaldehyde[195] was readily prepared by a standard procedure,[206] and reduction to 2,3-dimethoxybenzylamine[195] was accomplished using zinc and glacial acetic acid[207] at 55-70°. The reaction was sensitive to both water content and temperature. Using "wet" acetic acid (water content > 5%), significant quantities of non-basic material were obtained and identified from spectra (IR, NMR) as 2,3-dimethoxybenzyl alcohol. Use of higher temperatures (> 75°) gave the N-acetyl derivative of 2,3-dimethoxybenzylamine as a major product. The reduction was attempted with other reagents such as lithium aluminium hydride,[208,209] nickel aluminium alloy and aqueous sodium hydroxide,[197] or methanolic sodium borohydride and nickel(II) chloride,[210,211] but with less success. The change in the PMR spectrum of the hydrochloride of 2,3-dimethoxybenzylamine on deuteration was marked. The signals due to the aromatic protons collapsed from a multiplet (6.95 - 7.2 p.p.m.) to a singlet (7.1 p.p.m.) and the broad methylene signal at ca. 3.95 p.p.m. became a sharp singlet at 4.01 p.p.m.

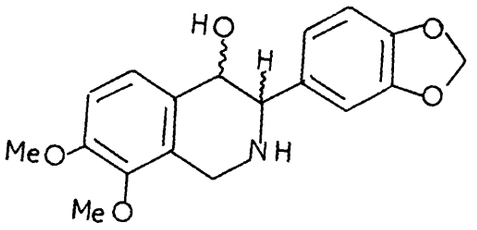
Condensation of the 2,3-dimethoxybenzylamine and the keto-acetal (352) was effected in toluene under reflux using a Dean and Stark water separator. The crude imine (359) was not purified, but was reduced in alcoholic solution with sodium borohydride to obtain a mixture of bases. Separation was easily effected by column chromatography to obtain the desired secondary amine (341).

The appearance of the PMR spectrum of (341) was very dependent on concentration. In "dilute" solution, signals for the [CH(OCH$_3$)] methine proton were observed as a doublet (4.22 p.p.m., J = 7 Hz), and signals for the [NH-CH] methine proton were presumed beneath those for the aromatic methyl ethers. However, in more concentrated solution, the methine protons were observed as a doublet (4.48 p.p.m., J = 7 Hz) and doublet of doublets (4.22 p.p.m., J = 7 Hz and 2 Hz). The smaller coupling was presumed due to the [-NH-] proton, though the "signal" due to the [NH] proton was observed as a broad signal (2.5 to 2.8 p.p.m.). In dilute solution, the signals due to the [CH-(OCH$_3$)] protons were observed as essentially a pair of singlets at 3.12 p.p.m. and 3.28 p.p.m., whereas in concentrated solution a series of four signals of approximately equal intensity were observed. It appeared that intermolecular hydrogen bonding was of significance in concentrated solution, whereas intramolecular hydrogen bonding predominated on dilution. Two major types of hydrogen bonded structures, (360) and (361) could be envisaged. The NMR spectra[212] of both 2,3-dimethoxybenzyl-aminoacetal (362; R=H) and the N-methyl derivative (362; R=Me) were very similar, and the signals for the methyl protons of the acetal group were observed as singlets in both cases, and the signals for the aromatic methoxyl protons were observed as two singlets with the same separation for both (362; R=H) and (362; R=Me), so hydrogen bonding of type (363), similar to (361), seemed unlikely to be of significance in an NMR sense.

Only partial N-methylation of (341) was achieved using formaldehyde and sodium borohydride, but near quantitative N-methylation was obtained using formaldehyde and formic acid, without significant cleavage of the acetal. In the PMR spectrum of the tertiary amine (364), no major changes were evident on dilution and the signals for the acetal methyl protons were observed as two three-proton singlets at 3.30 p.p.m. and 3.43 p.p.m. In dilute solution, the corresponding signals in the spectrum of the secondary amine (341) were observed at 3.12 p.p.m. and 3.28 p.p.m., whereas in concentrated solution, the four signals were found at 3.13, 3.22, 3.29 and 3.39 p.p.m., with the signals at 3.22 p.p.m. and 3.39 p.p.m. decreasing on dilution. These observations were considered further evidence for intramolecular hydrogen bonding for the secondary amine (341).

Ring closure of the secondary aminoacetal (341) was effected with 6N aqueous hydrochloric acid and the 3-aryl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (365) was obtained in poor (18%) yield. This compound proved resistant to hydrogenolysis, even in the presence of strong acids, and the aromatic 3-arylisoquinoline (366) was not obtained with ethanolic iodine, or with N-bromosuccinimide and subsequent treatment of the uncharacterized intermediate with strong mineral acids.

From the resistance of (365) to dehydration, it seemed likely that the C-3 hydrogen and C-4 hydroxyl were <u>cis</u> and not susceptible to antiperiplanar elimination. From interpretation of the PMR spectrum of (365), $J_{3H,4H} \leq 0$ Hz,



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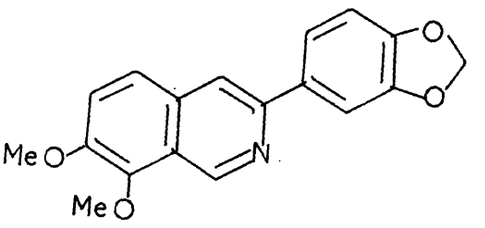

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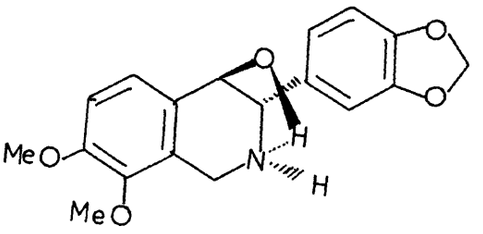

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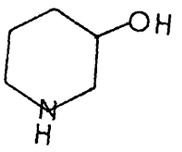

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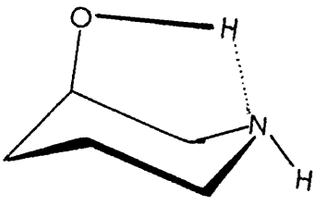

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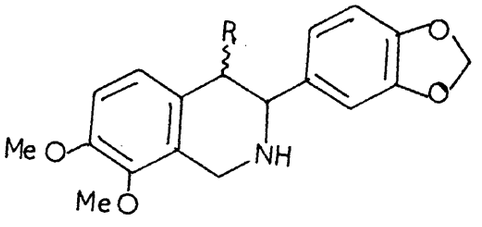

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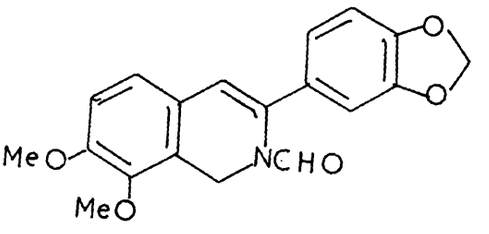


371

and the methylene protons at C-1 were observed as a doublet of doublets at 4.32 and 3.92 p.p.m. (J = 15 Hz). In the IR spectrum of (365) ($CHBr_3$), the absorptions at 3530 $cm.^{-1}$ and 3200 $cm.^{-1}$ did not change in position on dilution and that at 3530 $cm.^{-1}$ was attributed to an intramolecularly-bonded hydroxyl group. The results were consistent with the cis-3-equatorial-aryl, 4-axial-hydroxyl groups in an intramolecularly bonded conformer, such as (367) or the corresponding enantiomer, where the dihedral angle between $[C_3\text{-}H]$ and $[C_4\text{-}H]$ was measured on a Drieding model as about 80°.

In the example of 3-piperidinol (368), from spectroscopic studies it has been shown[213] that this compound exists in solution in the intramolecularly bonded form (369). Regrettably the problem of benzylic carbonium ions and possible formation of 4-alkoxy derivatives (vide infra) from the presence of alcohols was not appreciated at the time of these experiments and cyclizations were carried out in aqueous methanolic media. This almost certainly contributed to the problems of this reaction with the likely formation of 4-methoxy derivatives (370; R=OMe or OEt).

Hydrogenolysis cyclization mixture was also investigated in the hope of obtaining the tetrahydroisoquinoline (370; R=H), but without success. Chemical reductions of (365) were also investigated, and, by heating under reflux in formic acid[214] the hydroxyl group was removed but a mixture was obtained, which appeared to contain the N-formyl derivative of (370; R=H) and the N-formyl-1,2-dihydroiso-

quinoline (371). Presumably O-formylation and resultant loss of formate gave a carbonium ion at C-4, and the subsequent loss of the C-3 hydrogen was not therefore limited by stereochemical environment.

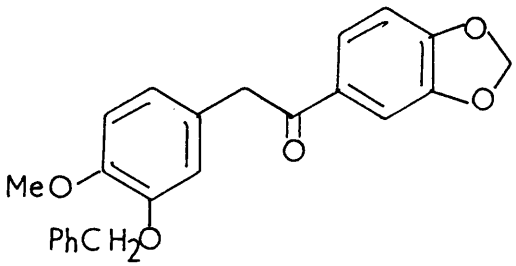
At this stage, quantities of materials - and yields - were small and concurrent investigations of the third route were far more promising, so attempts to obtain Berberastine by this route were abandoned.

The Deoxybenzoin route

Berbines, particularly 5-hydroxyberbines, have been obtained from 1,2-diarylethylamines,[29,42] as mentioned earlier, and a key step has been the reaction of an amine with glycidol[29] to afford a 3-aminopropan-1,2-diol. This type of reaction has been found to be difficult regarding yields and reproducibility. Condensation of aminoacetal with a deoxybenzoin and subsequent reduction was considered to be potentially better. Accordingly a route to the deoxybenzoin (372) was required.

Although many routes to ketones are known,[215] few seemed applicable to the preparation of a deoxybenzoin where the aryl groups differed. A full review of methods of obtaining deoxybenzoins has not been undertaken. A versatile route was considered desirable, and three such routes were considered.

A phosphorane, (373), derived from a benzyl halide, has been reacted[216,217] with benzonitrile (374) to afford,



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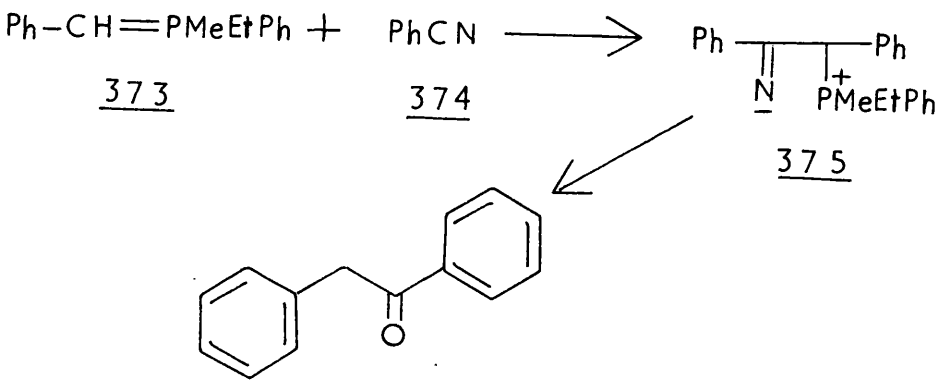

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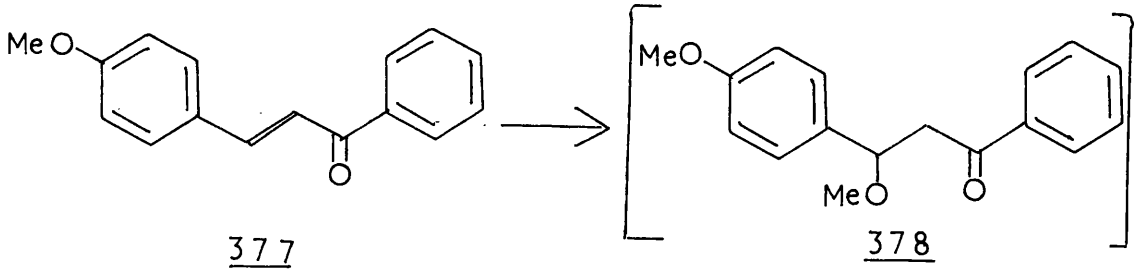

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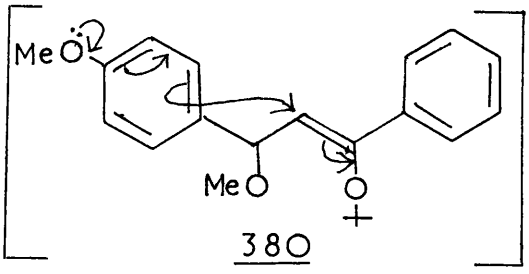

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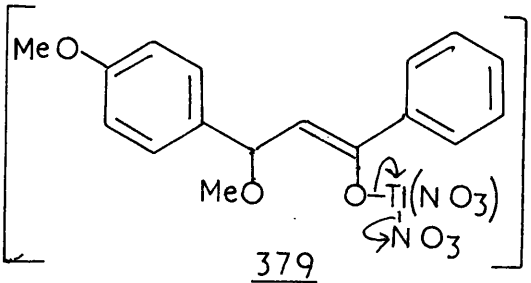

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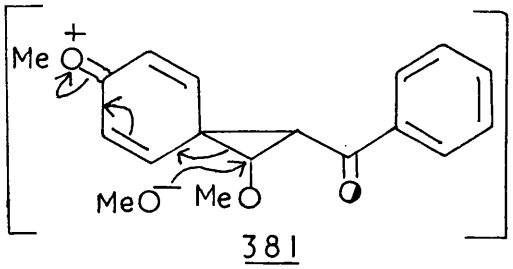

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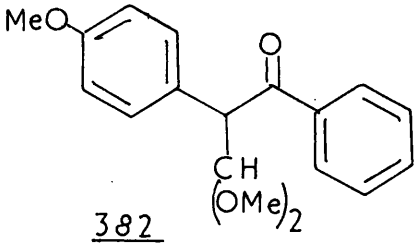

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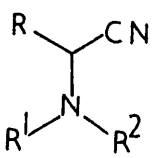
after base-promoted hydrolysis, deoxybenzoin (376). Suitable benzaldehydes are commonly available, and their conversion to benzyl halides and benzonitriles would afford necessary reagents so this route appeared interesting.

Rearrangement of chalcones, eg. (377), with thallium (III) nitrate in methanol was reported to afford[218,219] β-ketoacetals, eg. (382), which may be hydrolytically deformylated to deoxybenzoins in moderate yield. Since 3,4-methylenedioxyacetophenone had been prepared for other investigations, this route offered no problems regarding accessibility of starting materials.

The third route was that of alkylation of an α-aminonitrile.[220,221,222] Such alkylations with benzyl halides of α-aminonitriles derived from benzaldehydes, have been investigated by Hauser et al[220,221] and similar alkylations have been reported by Welvart.[222] Treatment of an N,N-dialkylaminonitrile (383) with a strong base, potassium amide, affords a carbanion (384), which may be alkylated to give (385). Thermal or base-promoted dehydrocyanation then gives an enamine (386) whereas hydrolysis gives a ketone (387). This route, because of its proven versatility, was chosen for investigation.

Before embarking on a synthesis of berberastine, the utility of the benzylation of an aminonitrile as a route to deoxybenzoins was briefly investigated. Preparation of N,N-diethyl-α-cyano-3,4-methylenedioxybenzylamine (388) was readily accomplished in high yield by modification of known procedures.[102,223,224] In the PMR spectrum of the aminonitrile



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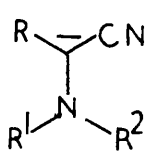

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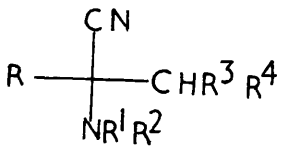

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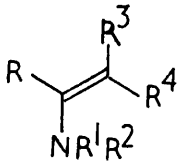

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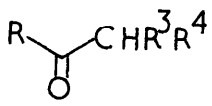

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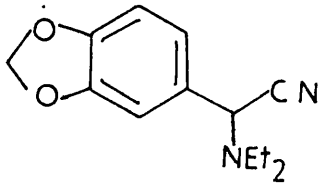

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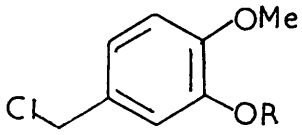

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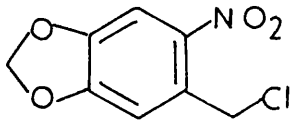

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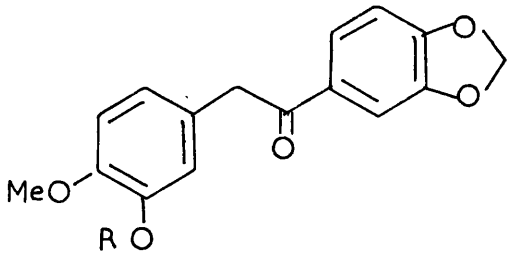

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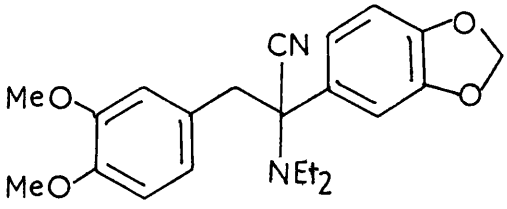

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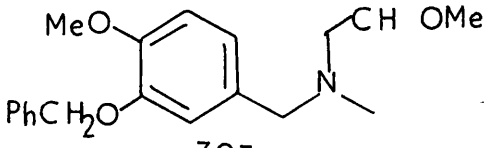
(388), the methylene protons of the diethylamino group gave rise to two quartets (2.53 and 2.61 p.p.m., J = 7.3 Hz) whereas only one triplet for both methyl groups was observed (1.07 p.p.m., J = 7.3 Hz).

The general procedure used for alkylations was to treat the aminonitrile (388) in DMF with sodium hydride under nitrogen, and, after several hours, to add the appropriate benzyl chloride. Evaporation of the resultant solution and stirring the residue in 2N sulphuric acid and dichloromethane overnight afforded the appropriate deoxybenzoin. Three benzyl halides were used, these being 3,4-dimethoxybenzyl chloride[225] (389; R=Me), 2-nitro-4,5-methylenedioxybenzyl chloride[226,227,228,229,230] (390) and 3-benzyloxy-4-methoxybenzyl chloride[231,232] (389; R=$PhCH_2$-). Moderate yields of the appropriate deoxybenzoins were obtained in each case and no attempts were made to optimize reaction conditions. In one case, alkylation with 3,4-dimethoxybenzyl chloride (389; R=Me), hydrolysis was only carried out for one hour and from the mixture of products both the deoxybenzoin (391; R=Me) and the alkylated aminonitrile (392) were isolated, and separate hydrolysis of (392) gave the deoxybenzoin (391; R=Me). In the PMR spectrum of (392), the benzylic methylene protons were found to be non-equivalent and signals were observed at 3.49 p.p.m. (J = 13 Hz) and 2.82 p.p.m. (J = 13 Hz). Two quartets for the methylene protons of the diethylamino group were again observed, at 2.77 p.p.m. and 2.80 p.p.m. (J = 7.5 Hz) at noticably lower field ($\triangle$ ca. 0.2 p.p.m.) than for the aminonitrile (388). The methoxyl protons gave rise to two

singlet signals, at 3.63 p.p.m. and 3.80 p.p.m., thus strong shielding operated, affecting the substituents at C-3 and C-4 to different degrees. The signals for the $\left[-OCH_2O-\right]$ protons though, were observed as a singlet at 5.93 p.p.m., this position being slightly higher than for those in (388) (5.99 p.p.m.). From the high field position (6.17 p.p.m.) and coupling constant (J = 2 Hz), this doublet was attributed to the $\left[C_2-H\right]$ proton. The expected position for this proton was calculated,[233] allowing only for the effect of the $\left[MeO\right]$ groups, as $\left[7.27-0.43-0.09\right]$, or 6.75 p.p.m. Thus an additional shielding effect of 0.58 p.p.m. remained unexplained. The $\left[C_6-H\right]$ proton was observed as a doublet of doublets (J = 2 Hz and 8.5 Hz) at 6.47 p.p.m., whereas a similar calculation as before would give the position as 6.81 p.p.m., with a difference of 0.34 p.p.m. Similarly, the difference between observed (6.70 p.p.m.) and calculated (6.75 p.p.m.) was 0.05 p.p.m. The shielding effect on the aromatic ring was not therefore, symmetrical along the 1-4 axis with free rotation. The gross effect was presumably due to the cyano group. If the methylenedioxyphenyl group were the cause a similar effect on that ring would be expected, but this was not observed. No explanation of the different shieldings at C-2 and C-6 is offered, other than conformational restrictions due to the 3-methoxyl group and the rest of the molecule.

Apart from providing a convenient route to deoxybenzoins, a notable application of the alkylation of aminonitriles has been to the synthesis of amines by Dyke and White.

For example, the use of methylaminoacetal in the preparation of aminoacetals gave such compounds as (393), and by alkylation with homopiperonyl chloride with subsequent thermolytic elimination of hydrogen cyanide the enamine (394) may be obtained.



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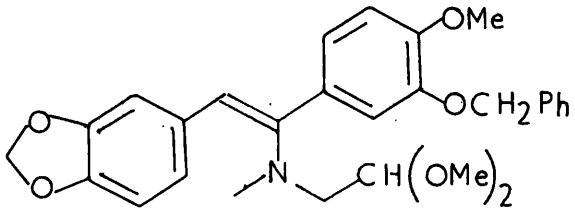

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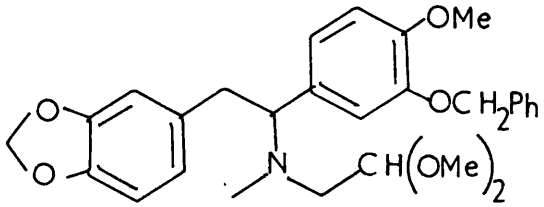

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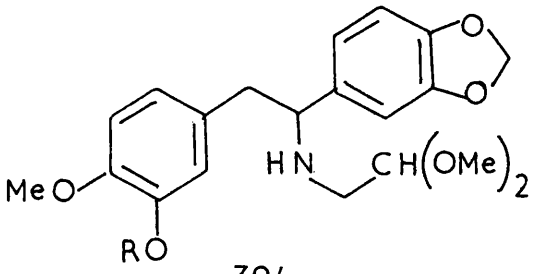
Reduction then afforded the aminoacetal (395). Aminoacetals of type (395) are key compounds in the syntheses of isopavines. No work has yet been reported on the use of benzyl halides bearing deactivating groups, such that the initially formed 1-benzyl-4-hydroxy-1,2,5,4-tetrahydroisoquinoline would not be susceptible to conversion to a pavine or isopavine.

Condensation of the deoxybenzoin (391; R=CH_2Ph) with aminoacetal was effected in toluene at reflux temperature and the resultant product was not isolated but reduced with ethanolic sodium borohydride to afford the aminoacetal (396; R=CH_2Ph) in 44% yield. Whether the uncharacterized intermediate was in the imine or enamine form was not determined. In the IR spectrum of the crude condensation product the absorption at 1670 $cm.^{-1}$ was approximately half that of pure deoxybenzoin (391; R=CH_2Ph) and it was concluded that the condensation was

only ca. 50% effective and was the limiting factor in the overall yield. Since this moderate yield was considered adequate no attempts were made to improve it. From the PMR spectrum of (396; R=CH_2Ph), it appeared that geminal methylene protons were equivalent since only simple AB couplings were observed and couplings involving the [NH] proton was not detected. In the IR spectrum of (396; R=CH_2Ph), the absorption at 3320 $cm.^{-1}$ was attributed to the [NH] group.

Removal of the phenolic benzyl group was readily accomplished by catalytic hydrogenation at atmospheric pressure using 10% Palladium on charcoal as catalyst. Both amines (396; R=CH_2Ph) and (396; R=H) were crystallized from petrols. In the IR spectrum of the phenolic amine (396; R=H), a weak absorption at 3300 $cm.^{-1}$ was attributed to the amino group by comparison with the precursor (396; R=CH_2Ph) and the strong absorption at 3520 $cm.^{-1}$ was attributed to the phenolic group. The PMR spectrum of (396; R=H) was noticably different to that of the precursor (396; R=CH_2Ph). The signals for the benzylic methylene protons were no longer observed as a doublet but as a multiplet and the protons were therefore non-equivalent and a concomitant complexity of the signals attributable to the benzylic methine proton was also evident. The broad signal at 2.0 p.p.m., attributed to the [NH] proton in the PMR spectrum of the precursor (396; R=CH_2Ph) was no longer evident. Instead a two-proton singlet was observed at 3.90 p.p.m. (deuterable), and was attributed to both the [OH] and [NH] protons.

The customary Pictet-Spengler cyclizations[234] of phenethylamines with aldehydes under acid conditions affords



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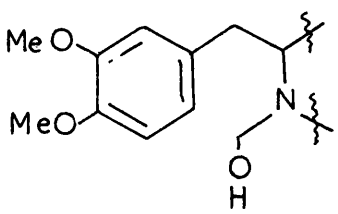

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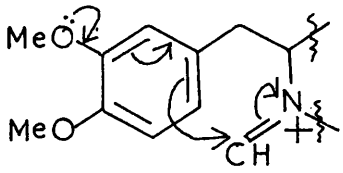

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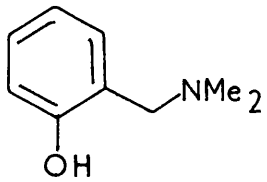

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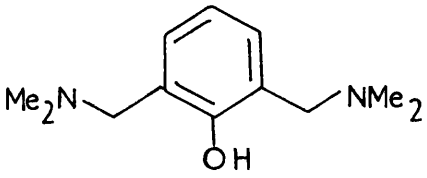

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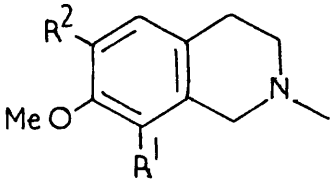

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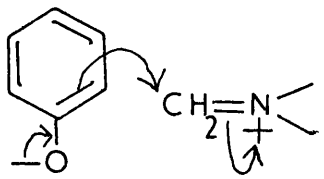

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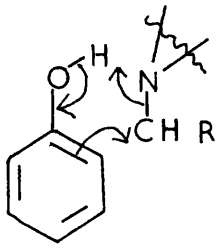

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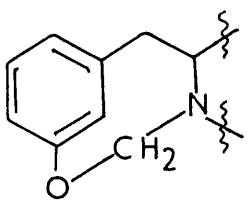

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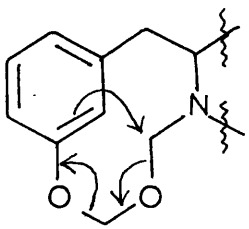


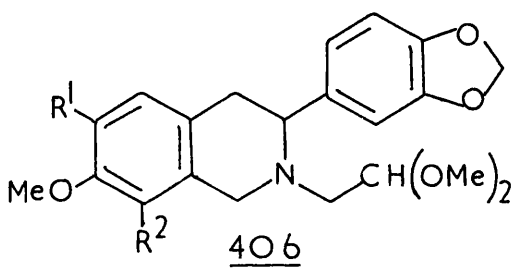
405

only ring closures *para* to an alkoxyl group, and some of the aspects of ring closures under neutral, or "physiological," conditions have been discussed earlier. The Pictet-Spengler reaction is a particular type of the more general Mannich reaction.[235,236,237] Reaction of formaldehyde with a phenethylamine first gives an N-hydroxymethyl derivative, eg. (397), which may be dehydrated to an iminium compound, and the latter is susceptible to nucleophilic attack as shown in (398).

Other examples of Mannich reactions involving phenols warrant consideration. Reaction between phenol, formaldehyde and dimethylamine was reported[238,239] to give both 2-N,N-dimethylaminomethylphenol (399) and 2,6-*bis*-(N,N-dimethylaminomethyl)phenol (400), illustrating the susceptibility of phenol to initial *ortho*- rather than *para*-substitution. A similar reaction of guaicol with formaldehyde and methylaminoacetal was reported[240] to give, after cyclization and hydrogenolysis, products resulting from both *para*-substitution (401; R^2=OH, R^1=H) (28%) and *ortho*-substitution (401; R^2=H, R^1=OH) (68%). Since such Mannich reactions and the "physiological" ring closures are carried out under approximately neutral or mildly basic conditions,[241] in contrast to the acidic conditions generally employed for the Pictet-Spengler reactions, contribution of phenoxide structures were considered. Thus a mechanism such as (402) could be postulated as providing the route to *ortho*- rather than *para*- ring closure.

Assuming that the relative signal positions of aromatic protons in PMR spectra of benzene derivatives are representative of relative electron densities, then the argument for phenoxides as key intermediates for ortho ring closure seemed weak. From investigations in DMSO, the change in position of an ortho proton on conversion of a phenol to a phenolate was reported[242,243] to lie in the range 0.42 to 0.59 p.p.m., whereas the para shift is 0.71 to 0.79 p.p.m. It has also been calculated that the charge density at the para position was greater than that at the ortho position for phenolates, though the reverse applied to phenols. It therefore seemed unlikely that the mechanism (402) is of significance in promoting ortho- rather than para- ring closure. Cyclic mechanisms such as represented by (403), have been proposed[244] to explain the preponderance of ortho-substituted products in the Mannich reaction of phenols, but this type of mechanism cannot be directly extrapolated to an intramolecular ring closure. The nearest simple analogies would require intermediates of type (404) or (405).

Reaction of the phenolic amine (396; R=CH_2Ph) with aqueous methanolic formaldehyde gave a mixture of products derived from both ortho- (406; R=OH, R^1=H) and para- (406; R=H, R^1=OH) ring closure and separation was effected by PLC to afford two compounds, A and B.



406

The PMR spectra of both A, (406; R=OH, R^1=H), and B, (406; R=H, R^1=OH), were very similar. In both cases the signals for the various methylene protons were observed as multiplets. Particularly noticable in both spectra were a group of four approximately evenly spaced signals at 2.4 to 2.7 p.p.m., showing signs of further fine splitting. By comparison with the precursor (396; R=H) it appeared that these signals were due to the $\left[N\text{-}C\underline{H}_2\text{-}CH(OCH_3)_2\right]$ methylene protons and presumably were part of an ABX pattern. For (406; R=OH, R^1=H), the highest-held signal in the aromatic range was observed at 6.62 p.p.m., whereas the corresponding signal for (406; R=H, R^1=OH) was observed at 6.54 p.p.m. The signal at 6.62 p.p.m. was attributed to the $\left[C_5\text{-}\underline{H}\right]$ proton, <u>para</u> to the phenolic group, and that at 6.54 p.p.m. was attributed to the $\left[C_5\text{-}\underline{H}\right]$ proton, <u>ortho</u> to the phenolic group. These signals were the most obvious differences between the PMR spectra of the two products of cyclization. The signals for the $\left[-OCH_2O-\right]$ protons 5.91 $\pm$ 0.01 p.p.m. were observed as a singlet in both cases. The signals for the acetal protons were, however, observed as two three-proton singlets at 3.28 p.p.m. and 3.21 p.p.m.

Infrared spectra in bromoform solution of (406; R=OH, R^1=H) and (406; R=H, R^1=OH) were significantly different in the range 800-1300 $cm.^{-1}$, the 'fingerprint' region, and permitted ready differentiation between the compounds.

Except for the difference in the 'aromatic' regions of the PMR spectra of the two products, it was not possible to assign

isomer structures to A and B with great certainty. The correctness of the assignments was born out by the eventual conversion of B, the 6-hydroxy compound (406; R=H, R^1=OH), to a known compound (vide infra), and from the results obtained by cyclization of the phenolic amine (396; R=H) with formaldehyde and formic acid. Under these conditions only one compound was isolated and this was presumed to be that resulting from para cyclization and was therefore (406; R=H, R^1=OH). This was identical with compound B. By TLC, a minor product of the same R_f as A, (406; R=OH, R^1=H), was detected and it appeared that, with formaldehyde and formic acid, a small amount of ortho ring closure occured. Such ortho closures have never been reported but this example was not confirmed by isolation and characterization. The use of TLC as a common analytical aid is a relatively recent inovation when compared with the history of isoquinoline chemistry and the tentative identification of an ortho ring closure under acidic conditions was not regarded as likely to be novel.

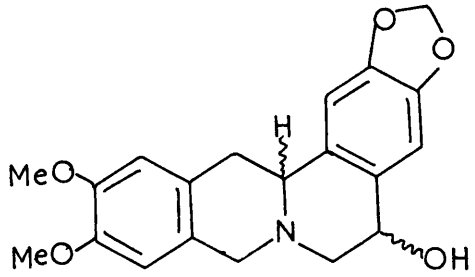
Both phenolic isoquinolines (406; R=H, R^1=OH) and (406; R=OH, R^1=H) were methylated by ethereal diazomethane in only moderate conversion but with high yield. Recovered starting materials were recycled several times through the methylation procedure to obtain satisfactory conversion.

In the PMR spectrum of the 7,8-dimethoxyisoquinoline (406; R=OMe, R^1=H) the aromatic protons were observed as a multiplet (6.6-7.0 p.p.m.) with only small unresolved multiplets at higher field positions than 6.8 p.p.m. For the

6,7-dimethoxyisoquinoline (406; R=H, R^1=OMe) a broad two-proton 'singlet' was observed at 6.60 p.p.m., and this was attributed to the $\left[C_5\text{-}\underline{H}\right]$ and $\left[C_8\text{-}\underline{H}\right]$ protons.

In the PMR spectra of all four tetrahydroisoquinolines, (406; R=OH or OMe, R^1=H) and (406; R=H, R^1=OH or OMe), a one-proton multiplet, partially resolved into a "doublet", was observed and was attributed to the $\left[C_{6}1\text{-}\underline{H}\right]$ proton. In a simple case of a 3,4-methylenedioxyphenyl system, the signals due to the $\left[C_6'\text{-}\underline{H}\right]$ proton would be expected as an uncoupled singlet, a doublet, or a doublet of doublets. The observed signals do not fit any such catagories though, since it appeared that the high-field part of the partially resolved "doublet" was weaker in intensity. This was considered indicative of the existence of conformers of (406), with discrete existence on the PMR time scale.

Cyclization of the 6,7-dimethoxy compound (406; R=H, R^1=OCH_3) was accomplished with 6N aqueous hydrochloric acid to obtain the known 9,10-dimethoxy-5-hydroxy-2,3-methylene-dioxyberbine (407). The PMR and IR spectra of (407) were

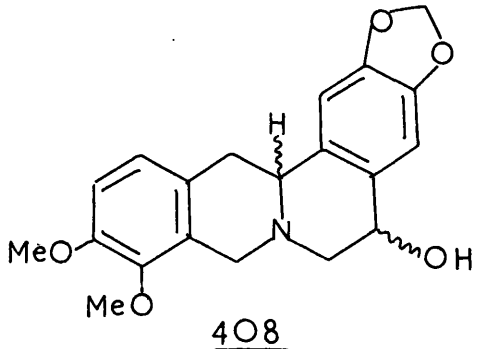


407

identical with those of (407) derived by another route, and there was no depression with a mixed melting-point. Hence

the structural assignment of B was further confirmed.

Cyclization of the 7,8-dimethoxy compound (406; R=OCH_3, R^1=H) was similarly effected with 6N aqueous hydrochloric acid to obtain 5-hydroxycanadine, or tetrahydroberberastine, (408) in 71% yield.



408

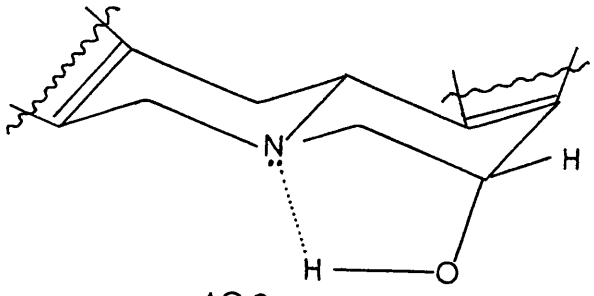
In the PMR spectrum of (408) ($CDCl_3$) (60 MHz) the signals for the methoxyl protons were observed as a six-proton singlet (3.86 p.p.m.), whereas they were observed as two three-proton singlets (3.78 and 3.82 p.p.m.) in the PMR spectrum of the hydrochloride of (408) $\left[(CD_3)_2SO\right]$ (100 MHz).

In the IR spectra of quinolizines, Bohlman bands at 2800 $cm.^{-1}$ are considered diagnostic for a <u>trans</u> configuration. Although absorptions in this region were observed for both (407) and (408), similar absorptions were also evident in the IR spectra of all of the amine precursors. Consequently the stereochemistry of the ring junction was not assigned.

Cyclization of the 7,8-dimethoxyisoquinoline derivative (406; R=OMe, R^1=H) was also carried out in a 1:1 solution of concentrated hydrochloric acid and ethanol. From examination of the reaction products by TLC, it appeared that three products

had been obtained, two of which were evident in (408) obtained by cyclization in aqueous acid. These two were presumably diastereoisomers due to different configurations of the hydroxyl group. A partial separation was effected by PLC and the IR spectra of the two fractions were identical except that for one (R_f 0.33), (α) a moderately sharp absorption at 3560 $cm.^{-1}$ was evident, and for the ether (R_f 0.19) (β) a broad absorption at 3250 $cm.^{-1}$ was evident. Thus the difference was one of intramolecular hydrogen bonding of the hydroxyl group to the nitrogen (409) (α) and of an unbonded hydroxyl group (410) (β).

The third component, faster moving on TLC, was also isolated by PLC. In the IR spectrum, no absorptions were evident above 3050 $cm.^{-1}$, and this compound did not contain an hydroxyl group and was not, for example, a cis-quinazoline isomer of (408). In the PMR spectrum, a three proton triplet (1.21 p.p.m., J = 7 Hz) and a two-proton quartet (3.64 p.p.m., J = 7 Hz) were evident, and the spectrum was otherwise similar to that of tetrahydroberberastine or 5-hydroxycanadine (408). A sample of 5-hydroxycanadine (408) was treated with ethanolic hydrogen chloride on a scale adequate for TLC, and after 18 hours the major component had the same R_f as the ethoxy-bearing compound. The third product of the cyclization in acid aqueous ethanol was therefore 5-ethoxycanadine (412). This presumably arose by O-protonation of the initially formed 5-hydroxycanadine, subsequent formation of the carbonium ion (411), and trapping (412) with ethanol.



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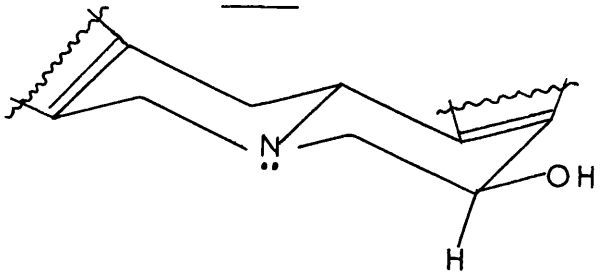

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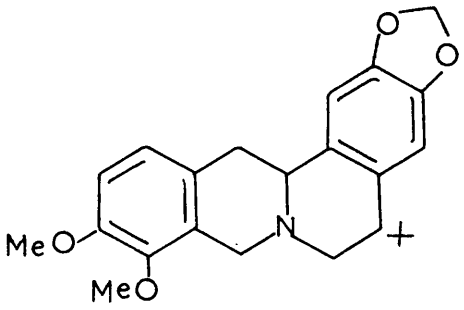

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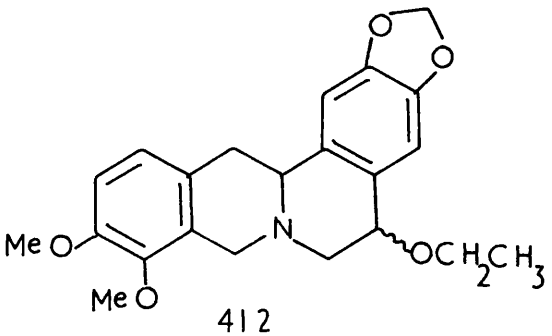

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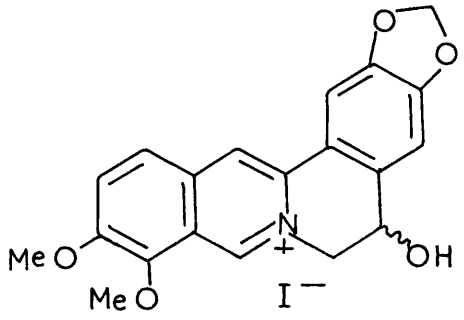

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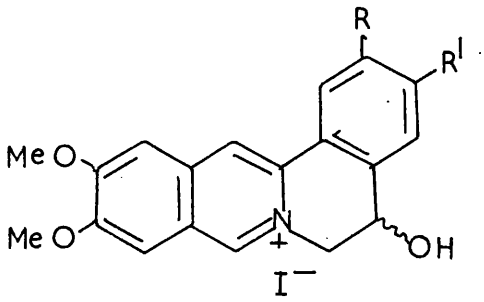

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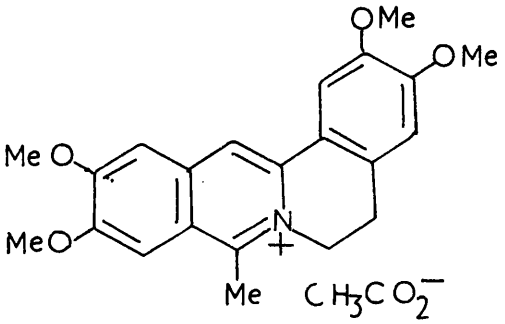

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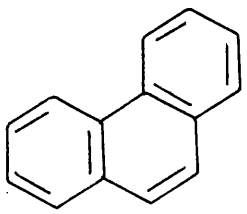


416

Tetrahydroberberastine (408) was dehydrogenated with ethanolic iodine in the presence of sodium acetate as buffer to afford (±) berberastine iodide (413).

It is interesting to compare the mass spectras of 5-hydroxycanadine (408), 5-ethoxycanadine (412), and the 10,11-dimethoxy isomer of 5-hydroxycanadine, (407). The first two compounds have fragmentation patterns similar to those of canadine, both compounds exhibiting hydrogen capture such that the loss of the 5-hydroxy- or 5-ethoxyl groups gave m/e 339, corresponding to canadine, with corresponding metastable peaks. Subsequent fragmentations bear a strong resemblance to that for canadine. In contrast, compound (407) gave an m/e 338, as previously reported. The line diagrams of (407), (408), (412), and canadine (150) are shown at the end of the experimental section. It would therefore seem that introduction of an hydroxyl or ethoxyl group at C-5 in a berbine does not dramatically change the fragmentation pattern and the observations and conclusions of Chen and Maclean[245] can be extrapolated to such 5-substituted berbines. This provides further confirmation of the relative structural assignments of the isoquinolines obtained by a chromatographic separation of isomers, rather than by an unambiguous synthesis.

Regrettably an authentic sample of berberastine iodide[5] was not available for comparison. The physical characteristics of the synthetic product were virtually identical with those reported for the natural product. A visual comparison of the IR spectra,[5] and comparison of UV data,[5,246] and the effect

of heating, all revealed no significant differences, and microanalytical data was consistent with structure (413). In addition a PMR spectrum was obtained.

The PMR data for some protoberberines in perdeutero-dimethylsulphoxide (DMSO-d^6) have been tabulated for comparison. A recent comparative study[247] of the PMR of protoberberines was, unfortunately, carried out using trifluoroacetic acid (TFA) as solvent. To illustrate the differences in chemical shifts obtained, the PMR data reported for berberine in both TFA and DMSO-d^6 [248] has been given. From comparison of the PMR spectra of berberine and tetradehydrocoralydine[248] (415), Santavy et al concluded that the signals at ca. $9\frac{1}{2}$ p.p.m. were attributable to the proton at C-13 rather than at C-8, since the lowest field signal for (415) was at 9.65 p.p.m., for a compound which did not have a proton at C-8. From studies in TFA, though, it was found that the lowest-field signal for 13-methyl-berberine was at 9.62 p.p.m., and that a signal at 8.44 p.p.m. in berberine was missing. Hence a reversal of relative assignments to protons at C-8 and C-13 was necessary, and this type of assignment has been favoured for berberastine and related 5-hydroxy compounds. For phenanthrene[249] (416), the signal for the proton at C-1 was reported to be at 8.93 p.p.m., a downfield shift of 1.66 p.p.m. relative to benzene. This proton is in a similar environment to that at C-13 in berbines and the chemical shift is also similar. From comparison of the protons at C-1 and C-4 in both (414; R + R^1 = $-OCH_2O-$) and (414; R=R^1=OMe), the effect of a methylenedioxy group was

Proton(s)	Berberastine	(414)[29] $R+R^1=OCH_2O$	(414)[29] $R=R^1=OMe$	Berberine[248]	Berberine[247] (in TFA)
$-OCH_2O-$(2,3)	6.20	6.2		5.98	6.10
2 x MeO(2,3)			3.8-4.1		
2 x MeO(9,10)	4.08, 4.12			3.81, 3.82	4.16, 4.29
2 x MeO(10,11)		4.05, 4.15	3.8-4.1		
H (1)	7.83	7.75	7.7	7.29	7.48
H (4)	7.16	7.15	7.15	6.76	6.90
H (8)	9.98	9.4	9.7	9.65	9.55
H (9)		7.75	7.7		
H (11)	8.02(d,			6.82 6.90	7.94 (d, 9 Hz)
H (12)	8.24(d,	7.75	7.7	7.04 7.12	8.05 (d, 9 Hz)
H (13)	9.01	8.85	8.95	8.30	8.44

similar to that of two methoxyl groups. If the chemical shift of the proton at C-1 for the unknown compound (414; $R=R^1=H$) is calculated,[233]

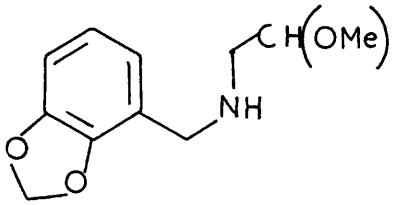
$$7.75 + 0.43 + 0.09 = 8.3 \text{ p.p.m.}$$

This value is ca. 0.6 p.p.m. higher field than that attributed to a proton at C-13, but additional peri interaction from the proton at C-12 could partly account for this. The apparently surprising observation of the high field position of the proton at C-11 (8.02 p.p.m.) in berberastine was presumably due to the position being para to the C-7,8 iminium system.

Benzo-[c]-phenanthridines

The first synthesis of sanguinarine, by Dyke et al, was by means[250] of the isoquinol-4-ylacetic acid (420) and this was obtained by cyclization of 2,3-methylenedioxybenzylamino-acetal (417) to the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (418), dehydration to the enamine (419) in situ, and condensation with glyoxylic acid to afford (420).

The aminoacetal (364) was subjected to an analogous series of reactions where the expected product was compound (421). Because of the betaine nature of the desired product, isolation of (421) was troublesome, so the crude mixture of organics, after extraction to remove non-quaternary bases, was reduced with sodium borohydride. It was hoped that the mixture contained the desired carboxylic acid (422; R=H). The mixture was worked up for acidic products and the material obtained was extracted from hydrochloric acid solution with chloroform



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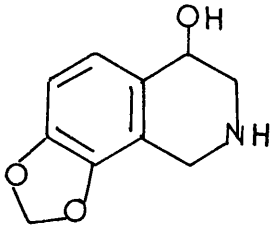

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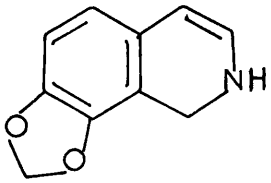

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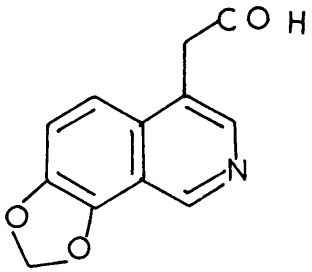

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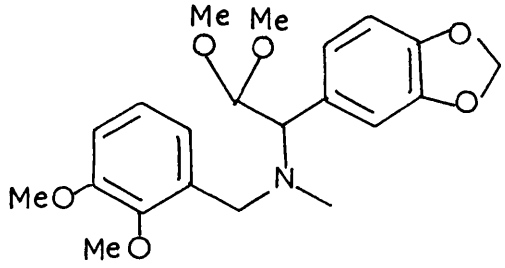

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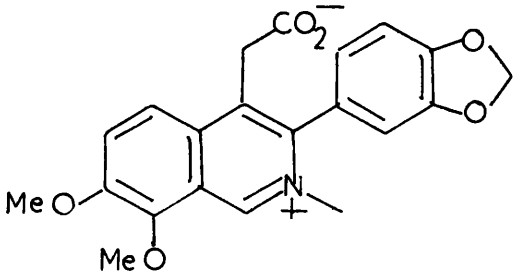

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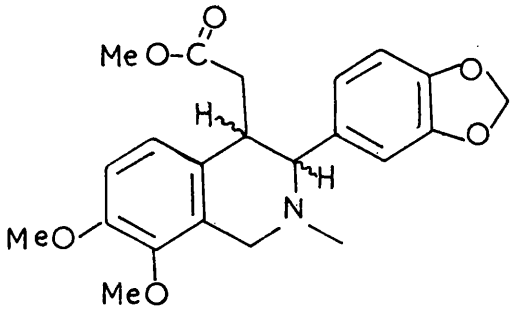

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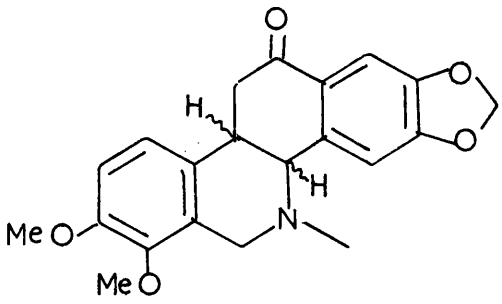

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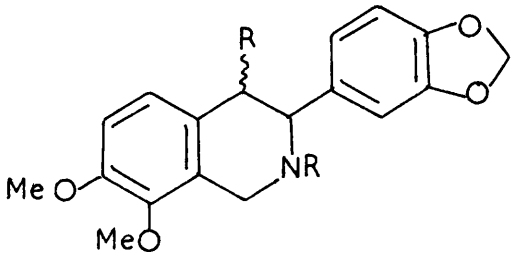


424

to obtain the crude acid (422; R=H). Characterization was effected by treatment with diazomethane to afford the ester (422; R=Me) and isolation as the hydrochloride salt in 19% yield from the aminoacetal (364).

In the PMR spectrum of (422; R=Me) the signals for the N-methyl protons were observed at 2.33 p.p.m. (15% of 3H) and 2.32 p.p.m. (85% of 2H). Whether the two signals were due to conformational or configurational isomers was not determined, since the relative stereochemistries at C-3 and C-4 was not ascertained. Whether the groups at C-3 and C-4 were cis or trans was not considered important at this stage. For example, future investigations could incorporate catalytic hydrogenation to facilitate generation of the desired cis stereochemistry, or epimerization at C-4 might be effected at a latter stage.

Cyclization of the ester (422; R=Me) was not attempted, mainly due to the small quantity of (422; R=Me) available. A successful cyclization would afford the ketophenanthridine (423), and conversion of (423) to homochelidonine would appear feasible.

It has been shown that the acetoxy group in a 4-acetoxy, 1,2,3,4-tetrahydroisoquinoline is susceptible to nucleophilic displacement, for example by cyanide ion to obtain a 4-cyano-1,2,3,4-tetrahydroisoquinoline.

The 3-aryl-4-hydroxy compound (424; R=H, R^1=OH) has been made, and since the condensation of the N-methyl aminoacetal (364) with glyoxylic acid was successful, then a similar cyclization to (424; R=Me, R^1=OH) must have occured. A

successful adaptation of the known replacement sequence of an hydroxyl- by a cyano-group to obtain (424; R=Me, R^1=CN) would be of great interest since this might permit annelation to a benzo-[c]-phenanthridine by known methods[251] to afford the desired oxygenation pattern.

It was concluded that the aminoacetal route to a 3-aryl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline could be of value as a synthetic approach to hexahydrobenzo-[c]-phenanthridines.

EXPERIMENTAL

Both IR and UV spectra were measured on various spectrophotometers. NMR spectra were recorded with a Varian A-60 spectrometer unless otherwise stated. Melting points are uncorrected. Evaporations of all solvents of boiling point less than 110° were carried out at 40°, using a water pump and a rotary evaporator.

2,3-Dimethoxy-6-iodobenzoic acid (299; R=OMe).

a) Thallium (III) oxide (42.0 g., 0.184 mol) was dissolved in trifluoroacetic acid (200 ml) by heating at reflux for two days. To the cooled solution was added 2,3-dimethoxybenzoic acid (20.0 g., 0.11 mol) and the resultant solution was heated under reflux for 5 hours. The solvent was removed by distillation and the residual oil was stirred with dichloromethane (200 ml) and 2N potassium iodide (500 ml) for ca. 0.5 hour. Sodium bisulphite was added to the red mixture until a light yellow colour was obtained. The mixture was filtered and the residue was washed with dichloromethane and the filtrates were combined. The organic phase was separated and washed successively with water (100 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated to dryness to obtain a pale red oil (ca. 34 g.), crystallization of which from chloroform/petrol gave 2,3-dimethoxy-6-iodobenzoic acid (299; R=OMe) (28.1 g., 83%) as an off-white solid, m.p. 136-137°, analytical sample (from chloroform/petrol) m.p. 137-138°, (lit.[150] m.p. 137-138°);

$\nu_{max.}$($CHBr_3$) ($cm.^{-1}$) 1715 (CO.O), 810 (1,2,3,4-tetra-substituted benzene); NMR ($CDCl_3$) 3.85 (3H, s; $\underline{CH_3}O-C_3$), 3.90 (3H, s; CH_3O-C_2); 6.71 (1H, d; J = 8.5 Hz, $C_4-\underline{H}$); 7.50 (1H, d; J = 8.5 Hz, $C_5-\underline{H}$); 9.6 (1H, s, removed by D_2O; $-CO_2-\underline{H}$) (Found: C, 34.8; H, 3.4; I, 42.0. $C_9H_9IO_4$ requires C, 35.1; H, 3.0; I, 41.2%).

b) Thallium (III) oxide (33.0 g., 0.144 mol) was dissolved in trifluoroacetic acid (150 ml) by heating at reflux for two days. To the cooled solution was added 2,3-dimethoxy-benzoic acid (15.7 g., 86 mmol) and the reaction was carried out as before to obtain, after crystallization from chloroform/petrol, an off-white solid (20.0 g.) which was (by examination of PMR spectrum) a mixture of 2,3-dimethoxy-benzoic acid and 2,3-dimethoxy-6-iodobenzoic acid (299; R=OMe) in 1:1 molar ratio. The mixture was dissolved in methanol (300 ml.) and the solution was saturated with hydrogen chloride and heated under reflux for 3 hours, then evaporated to dryness. The residue was shaken with ether (150 ml) and saturated aqueous sodium bicarbonate solution (3 x 50 ml). The combined aqueous extracts were acidified with 36% w/w hydrochloric acid and extracted with chloroform (2 x 50 ml). The combined chloroform extracts were washed with water (2 x 50 ml), brine (50 ml), and dried (Na_2SO_4) and evaporated to dryness to afford 2,3-dimethoxy-6-iodobenzoic acid (12.0 g., 45%) m.p. 136-137°, mixed m.p. with sample obtained by route (a) 136-137°. Spectra data were identical with those obtained for (299; R=OMe) by route (a).

Methyl 2,3-dimethoxy-6-iodobenzoate.

Ethereal diazomethane was added to a solution of 2,3-dimethoxy-6-iodobenzoic acid (299; R=OMe) (11.0 g., 36 mmol) in methanol (100 ml) and the yellow solution was kept at ambient temperature for 16 hours, purged with nitrogen for 1 hour, and evaporated to dryness. The residue was dissolved in ether (200 ml) and washed successively with saturated aqueous sodium bicarbonate solution (2 x 50 ml), water (50 ml), brine (2 x 50 ml) and dried (Na_2SO_4) and evaporated to dryness to afford methyl 2,3-dimethoxy-6-iodobenzoate (11.0 g., 95%), m.p. 57-59°; $\lambda_{max.}$(nm) (ϵ) (EtOH) 236 (12,500), 290 (2,300), $\lambda_{inflex.}$287.5 (2,320); $\nu_{max.}$($cm.^{-1}$) (nujol) 1725; NMR ($CDCl_3$) 3.83 (3H, s; C_3-O$\underline{CH_3}$); 3.93 (3H, s; C_2-O$\underline{CH_3}$); 6.69 (1H, d; J = 8.5 Hz; C_4-$\underline{H}$); 7.42 (1H, d, J = 8.5 Hz; C_5-$\underline{H}$) (Found: C, 37.0; H, 3.2; I, 39.0. $C_{10}H_{11}IO_4$ requires C, 37.3; H, 3.4; I, 39.4%).

8-Hydroxy-7-methoxy-3-(3,4-methylenedioxyphenyl)isocoumarin (317).

Sodium hydride (50% oil dispersion, 2.38 g., 49.5 mmol) was washed with petrol (60-80°, 3 x 100 ml) under nitrogen. Dry dimethylformamide (150 ml) was added, followed by 3,4-methylenedioxyphenylbutan-2,4-dione (9.70 g., 47.1 mmol), 2,3-dimethoxy-6-iodobenzoic acid (13.80 g., 44.8 mmol) and copper powder (0.50 g.). The mixture was heated under reflux for 7.5 hours, stood at 21° for 16 hours, and evaporated to dryness. The resultant black oil was stirred with dichloromethane (1.5 litres) and 0.5N hydrochloric acid (1 litre) and

filtered. The organic phase was washed with 0.2M potassium carbonate solution (500 ml), dried (Na_2SO_4), and evaporated to dryness to afford a black tar (ca. 20 g.). Extraction of the tar with hot petrol (60-80°, 3 x 200 ml) left a gummy dark solid which was stirred with carbon tetrachloride (200 ml), filtered, and the residue was washed with more carbon tetrachloride and dried to obtain crude (317) (suitable for subsequent reactions) (8.76 g., 28.1 mmol., 62.8%) as a pale brown solid. Sublimation of the crude product at 206° 0.07 mm Hg gave 8-hydroxy-7-methoxy-3-(3,4-methylenedioxyphenyl)isocoumarin (317) (75% recovery) as a very pale green solid, m.p. 217-218°; $\lambda_{max.}$(nm) (ε) (MeOH) 231 (29,500), 323 (22,900), 377 (13,500), $\lambda_{inflex.}$ 264 (10,100); $\lambda_{max.}$(nm) (ε) (CH_2Cl_2) 238 (25,500), 327 (21,200), 378 (13,500), $\lambda_{min.}$ 280 (6,640), 354 (10,400), $\lambda_{inflex.}$ 259 (11,100), 269 (9,340); $\nu_{max.}$(KBr)(cm.$^{-1}$) 1670 (CO.O), 930 (OCH_2O), $\nu_{max.}$($CHBr_3$) 2840 (OMe) 1655 (CO.O) 940 (OCH_2O); NMR (DMSO-d^6) (100 MHz) 3.86 (3H, s; Ar$O\underline{CH}_3$); 6.10 (2H, s; -$O\underline{CH}_2O$-); 7.03 (1H, d, J = 9 Hz; C_6-$\underline{H}$ or C_5'-$\underline{H}$); 7.08 (1H, d, J = 9 Hz; C_5'-$\underline{H}$ or C_6-$\underline{H}$); 7.30 (1H, s; C_2'-$\underline{H}$); 7.33 (1H, d of d, J = 9 and 2.5 Hz; C_5-$\underline{H}$); 7.37 (1H, d, J = 2.5 Hz; C_4-$\underline{H}$); 7.53 (1H, d, J = 9 Hz; C_6'-$\underline{H}$) (Found: C, 65.6; H, 4.1. $C_{17}H_{12}O_6$ requires C, 65.4; H, 3.9%).

7,8-Dimethoxy-3-(3,4-methylenedioxyphenyl) isocoumarin (302; R=OMe).

Pure sublimed 8-hydroxy-7-methoxy-3-(3,4-methylenedioxyphenyl) isocoumarin (317) (0.250 g., 0.80 mmol), potassium carbonate (0.280 g., 2.00 mmol) and iodomethane (2 ml) in

dimethylformamide (25 ml) was stirred for 2 days at 21° and the mixture was evaporated to near dryness. The residue was shaken with dichloromethane (60 ml) and washed with water (4 x 20 ml) and brine (20 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was washed thoroughly with dry ether and dried to afford 7,8-dimethoxy-3-(3,4-methylenedioxyphenyl) isocoumarin (302; R=OMe) (0.260 g., 99.5%) as a pale yellow solid, m.p. 216-217°; $\lambda_{max.}$(nm) (ε) (MeOH) 228.5 (29,200), 320.5 (24,000), 371.5 (11,200), $\lambda_{inflex.}$259.5 (7,720), 328.5 (22,200); $\nu_{max.}$(cm.$^{-1}$) ($CHBr_3$) 2845 (OMe), 2780, 1725 (CO.O), 940 (OCH_2O); NMR (DMSO-d^6) (100 MHz) 3.84 (3H, s; C_7-O$\underline{CH}_3$); 3.90 (3H, s; C_8-O$\underline{CH}_3$); 6.05 (2H, s; -O$\underline{CH}_2$O-); 6.97 (1H, d, J = 9 Hz; C_5'-$\underline{H}$); 7.10 (1H, s; C_2'-$\underline{H}$); 7.2-7.45 (2H, m; C_6-$\underline{H}$ and C_6'-$\underline{H}$) 7.32 (1H, s; C_4-$\underline{H}$); 7.57 (1H, d, J = 9 Hz; C_5-$\underline{H}$) (Found: C, 66.1; H, 4.6. $C_{18}H_{14}O_6$ requires C, 66.3; H, 4.3%).

2-Ethoxybenzoic acid.

Both 2-iodobenzoic acid (4.97 g., 20 mmol) and 1-(3,4-methylenedioxyphenyl)butan-1,3-dione (4.12 g., 20 mmol) were added to a solution, prepared by addition of sodium (ca. 1.2 g., ca. 52 mmol) in ethanol (30 ml), followed by copper powder (0.20 g.) and the mixture was heated under reflux for 3.5 hours. The cooled mixture was filtered and the filtrate was evaporated to dryness. The residues were combined, stirred with chloroform (100 ml) and water (100 ml) and filtered. The organic phase was washed with water, dried (Na_2SO_4) and evaporated to dryness. The residue (2.25 g.) was extracted with hot petrol (60-80°,

3 x 50 ml) and the combined petrol extracts were cooled and filtered to obtain 3,4-methylenedioxyacetophenone (2.06 g., 63%) as a pale yellow solid, m.p. 80-82°, mixed m.p. 80-82° (IR and NMR spectra were identical with sample obtained by acylation of methylenedioxybenzene; vide infra).

The basic aqueous solution remaining after extraction with chloroform was acidified with 2N hydrochloric acid and extracted with chloroform. The organic phase was washed with water (50 ml), brine (50 ml), dried (Na_2SO_4) and evaporated to dryness. The residue (4.25 g.) was stirred with benzene, filtered, washed with benzene, and the combined filtrates were evaporated to dryness. The residue was extracted with hot petrol (60-80°) by decantation and the petrol solution was diluted with ethyl acetate and extracted with 2N sodium hydroxide (2 x 40 ml). The combined extracts were acidified with 36% hydrochloric acid and the mixture was extracted with ether (3 x 50 ml). The combined ethereal extracts were washed with water (2 x 50 ml), brine (50 ml), dried (Na_2SO_4) and evaporated to dryness to obtain 2-ethoxybenzoic acid (2.99 g., 90%) m.p. ca. 10-15° (lit.[165] 19°), $\nu_{max.}$ ($cm.^{-1}$) (film), 3200 (very broad, CO_2H), 1690 (CO_2H), 750; NMR ($CDCl_3$) 1.49 (3H, t, J = 7 Hz; CH_2-$\underline{CH_3}$); 4.23 (2H, q, J = 7 Hz; -$O\underline{CH_2}CH_3$); 7.0-8.0 (3H, m; C_3-$\underline{H}$, C_4-$\underline{H}$, C_5-$\underline{H}$); 8.10 (1H, d of d, J = 8 Hz and 1.5 Hz; C_6-$\underline{H}$) (Found: C, 65.4; H, 5.7. $C_9H_{10}O_3$ requires C, 65.0; H, 6.0%).

Attempted preparations of 7,8-Dimethoxy-3-(3,4-methylene-dioxyphenyl) isocoumarin (302; R=OMe) in alcohols.

a) 2,3-Dimethoxy-6-iodobenzoic acid (299; R=OMe) (616 mg., 2.0 mmol) and (3,4-methylenedioxyphenyl)butan-1,3-dione (300) (412 mg., 2.0 mmol) were added to 0.5N sodium ethoxide in ethanol (15 ml), followed by copper (II) acetate (70 mg., 0.5 mmol) and the mixture was heated under reflux for 3.5 hours, then evaporated to dryness. The residue was shaken with water (solution A) and chloroform for 2 hours, filtered, and the organic phase was washed with aqueous sodium bicarbonate (3 x 20 ml), water (20 ml), dried (Na_2SO_4), and evaporated to dryness to afford a yellow solid (338 mg.). The solid was extracted with boiling petrol (60-80°) and the extracts were cooled and filtered and the residue was dried to give 3,4-methylenedioxyacetophenone (200 mg., 61%).

Solution A was acidified with 2N hydrochloric acid and extracted with chloroform. The chloroform solution was washed with water, dried (Na_2SO_4) and evaporated to dryness to afford a buff solid (acids fraction) (552 mg.), the NMR spectrum of which is reproduced in part in the spectra section.

b) A similar experiment was carried out in t-butanol using potassium t-butoxide as base, with a similar work-up procedure. The NMR spectrum of the acids fraction is reproduced in part in the spectra section.

c) A similar experiment was carried out in methanol with sodium methoxide as base, with a similar work-up procedure. The NMR of the acids fraction is reproduced in part in the spectra section.

Methylenedioxybenzene.

A solution of catechol (220 g., 2.00 mol) in dimethylsulphoxide (180 ml), total volume 360 ml., was added in eighteen 20 ml portions, at 4 minute intervals, with simultaneous addition of sodium hydroxide pellets (9.2 g. portions, total 165.6 g., 4.14 mol), to a stirred solution of dichloromethane (220 ml) in dimethylsulphoxide (400 ml) heated to reflux (105°) under nitrogen. Dichloromethane (50 ml) was added after reaction time of 75 minutes, and again (50 ml) after a further 20 minutes. Water was then added in portions (100 ml) with concurrent distillation (b.p. ca. 110°) such that the total volume of the reaction mixture remained approximately constant. After 1.4 litres of colourless distillate was collected, the organic phase in the distillate was separated and the aqueous phase was extracted with ether (1 x 200 ml., 2 x 100 ml). The combined organic phases, derived from the distillate, were dried ($MgSO_4$), and ether was removed by distillation under reduced pressure (water pump) at 21°. The colourless residual oil was distilled to afford methylenedioxybenzene (210 g., 86%) b.p. 62°/11 mm Hg (lit.[160] b.p. 74°/22 mm Hg).

3,4-Methylenedioxyacetophenone.

Perchloric acid (60%, 1.2 ml) was added to a solution of methylenedioxybenzene (100 g., 0.82 mol) and acetic anhydride (200 ml) and the black solution was heated on a steam bath for 30 minutes, cooled, and stirred with aqueous sodium

carbonate for 1 hour. The mixture was extracted with dichloromethane (1 x 500 ml., 2 x 50 ml) and the combined extracts were washed with water (100 ml), dried (Na_2SO_4), and evaporated to dryness at reduced pressure (water pump) at 30°. The resultant black tar was extracted with boiling petrol (60-80°, 6 x 500ml) and the combined extracts were cooled and filtered. The filtrate was concentrated to 200 ml by distillation of solvent at reduced pressure at 30°. The mixture was filtered and the combined residues were washed with petrol (40-60°, 100 ml) and dried to afford 3,4-methylenedioxyacetophenone (74.3 g., 55.5% conversion) as a pale yellow solid, m.p. 83-84° (lit.[252] m.p. 84-85°); $\lambda_{max.}$(nm) (ϵ) (EtOH) 228.5 (17,300), 272 (6,300), 308 (7,400); $\nu_{max.}$($cm.^{-1}$) ($CHBr_3$) 2880 (CH_3), 1675 (C=O), 930 (OCH_2O); NMR ($CDCl_3$) 2.50 (3H, s; $CO\underline{CH_3}$); 6.78 (1H, d, J = 8 Hz; C_5-$\underline{H}$); 7.38 (1H, d, J = 2 Hz; C_2-$\underline{H}$); 7.52 (1H, d of d, J = 8 and 2 Hz; C_6-$\underline{H}$).

N-(2,2-Dimethoxyethyl)-2,3-dimethoxy-6-(3,4-methylenedioxyphenacyl) benzamide (319).

A suspension of 7,8-dimethoxyisocoumarin (15.7 g., 48.2 mmol) in aminoacetal (20 ml) and dimethylsulphoxide (150 ml) was stirred for 2 weeks at ca. 20°. The light red solution was poured into water (2 litres) and extracted with ether (3 x 300 ml). The combined ethereal extracts were stood for 1 hour and filtered. The residue was washed with dry ether (2 x 10 ml) and dried to obtain N-(2,2-dimethoxy-

ethyl)-2,3-dimethoxy-6-(3,4-methylenedioxyphenacyl) benzamide (319) (5.60 g., 13.0 mmol., 27%) m.p. 132.5-133.5°. The ethereal filtrate was evaporated to dryness and the residue was washed with dry ether (2 x 10 ml) and dried to afford (319) (2.30 g., 5.3%) as an off-white solid, m.p. 129-130°. The aqueous dimethylsulphoxide solution was extracted with dichloromethane (3 x 300 ml) and the combined extracts were washed with water (1 x 2 litres, 2 x 1 litre) and dried (Na_2SO_4) and evaporated to dryness. The residue was triturated with ether to obtain a further sample of (319) (2.20 g., 5.1%) as a very pale brown solid, m.p. 129-130°. (Total yield 10.1 g., 23.5 mmol, 48.7%), analytical sample, m.p. 132.5-133.5°; $\lambda_{max.}$(nm) (ε) (EtOH) 205 (48,800), 230 (29,700), 278 (9,150), 314 (9,150), $\lambda_{min.}$220 (24,400), 252 (2,290), 294 (6,870); $\nu_{max.}$($cm.^{-1}$) ($CHBr_3$) 3420 (broad, m, NH), 2850 (OCH_3), 1690-1650 (carbonyls), 940 (OCH_2O); NMR ($CDCl_3$) 3.32 (6H, s; $CH(O\underline{CH}_3)_2$); 3.37 (2H, apparent t, J ≃ 5.5 Hz; -NH $\underline{CH}_2$-$\underline{CH}$-); 3.86 (6H, s; 2 x Ar$O\underline{CH}_3$); 4.30 (2H, s; Ar$\underline{CH}_2CO$); 4.38 [1H, t, J = 5.5 Hz; $CH_2\underline{CH}(O.CH_3)_2$]; 6.02 (2H, s, -$O\underline{CH}_2O$-); 6.54 (1H, broad t, J ≃ 5.5 Hz; -$\underline{NH}$); 6.86 (1H, d, J = 8 Hz; C_5'-$\underline{H}$); 6.89 (2H, s; C_4-$\underline{H}$ and C_5-$\underline{H}$); 7.50 (1H, d, J = 1.5 Hz; C_2'-$\underline{H}$); 7.68 (1H, d of d, J = 1.5 and 8 Hz; C_6'-$\underline{H}$) (Found: C, 61.3; H, 5.8; N, 3.2. $C_{22}H_{25}NO_8$ requires C, 61.25; H, 5.8; N, 3.25%).

Attempted preparations of 7,8-dimethoxy-2-(2,2-dimethoxyethyl)-3-(3,4-methylenedioxyphenyl) isocarbostyril (303; R=OMe).

a) A solution of N-(2,2-dimethoxyethyl)-2,3-dimethoxy-6-(3,4-

methylenedioxyphenacyl) benzamide (319) (0.95 g., 2.21 mmol) in benzene (60 ml) was heated under reflux for 16 hours under a Dean and Stark head. Evaporation of the solvent afforded the starting material as an off-white solid, m.p. 132-133°. Mixed m.p. 132-133°.

b) A similar reaction to (a), but using xylene as solvent and adding tri-n-butylamine (0.1 ml) also afforded only the starting material, (319).

c) A solution of (319) (0.60 g., 1.40 mmol) in dimethylformamide (20 ml) was heated under reflux for 2 days, then evaporated to dryness. The residue was dissolved in ethyl acetate - ether (1:1) (50 ml) and the solution was washed with water (3 x 10 ml), brine (2 x 10 ml), dried (Na_2SO_4), and evaporated to dryness to afford a red gum. Trituration of the gum with dry ether gave the starting material (319) (0.40 g., 66% recovery) as a buff solid, m.p. 129-130°. Evaporation of the ethereal solution gave a red tar (0.15 g.), multicomponent by TLC investigation. Attempted separation of components by PLC was unsuccessful.

N-(2,2-Dimethoxyethyl)-2,3-dimethoxy-6-[2-hydroxy-2-(3,4-methylenedioxyphenyl)ethyl] benzamide (324; R=H).

To a solution of N-(2,2-dimethoxyethyl)-2,3-dimethoxy-6-(3,4-methylenedioxyphenacyl) benzamide (319) (2.69 g., 6.44 mmol) in 95% ethanol (80 ml) was added sodium borohydride (2.0 g.) and the solution was stirred for 2 hours, then evaporated to near dryness. Chloroform (50 ml) and water

(60 ml) were added and the organic phase was washed with water (2 x 30 ml) and dried (Na_2SO_4) and evaporated to dryness to give a pale yellow gum. Crystallization from benzene (50 ml) and petrol (60-80°, 60 ml) gave N-(2,2-dimethoxyethyl)-2,3-dimethoxy-6-[2-hydroxy-2-(3,4-methylenedioxyphenyl)ethyl]-benzamide (324; R=H) (2.53 g., 94%), m.p. 121-122°; $\lambda_{max.}$(nm) (ε) (EtOH) 205 (57,700), 287 (6,340), $\lambda_{min.}$258 (1,000), $\lambda_{inflex.}$231 (13,900); $\nu_{max.}$($cm.^{-1}$) ($CHBr_3$) 3420 (s, sh, NH), 3300 (broad, s, OH), 2850 (w , OMe), 2790 (w), 1645 (CONH), 940 (OCH_2O); NMR ($CDCl_3$) 3.86 (6H, s; 2 x $ArO\underline{CH_3}$); 4.0-4.3 (1H, broad, removed by D_2O; $O\underline{H}$); 4.50 (1H, t, J = 5 Hz; -$\underline{CH}$-OH); 4.74 (1H, broad t, J ≃ 7Hz; $NHCH_2\underline{CH}$-); 5.95 (2H, s; -$O\underline{CH_2}O$-); 6.63 (1H, broad t, J ≃ 7 Hz; -$\underline{NH}$); 6.75-7.0 (5H, m, aromatics) (Found: C, 61.05; H, 6.1; N, 3.4. $C_{22}H_{27}NO_8$ requires C, 61.0; H, 6.3; N, 3.2%).

Attempted preparation of N-(2,2-dimethoxyethyl)-2,3-dimethoxy-6-[2-hydroxy-2-(3,4-methylenedioxyphenyl)ethyl]benzylamine (320).

a) Lithium aluminium hydride (0.25 g.) was added to a solution of N-(2,2-dimethoxyethyl)-2,3-dimethoxy-6-(3,4-methylenedioxyphenacyl)benzamide (0.30 g., 0.70 mmol) in dry tetrahydrofuran (40 ml) and the mixture was heated under reflux for 1.5 hours. An aqueous solution of sodium potassium tartrate was added dropwise to the stirred, cooled mixture, then filtered, and the residue was washed with tetrahydrofuran. The combined filtrates were evaporated to near dryness and the residue was shaken with ether (40 ml) and water. The ethereal solution was extracted with ice-cold 2N sulphuric acid (3 x 10 ml) and the extracts

were combined to give solution A. The ethereal solution was washed with saturated aqueous sodium bicarbonate (30 ml), water (30 ml), dried (Na_2SO_4), and evaporated to give the hydroxy-amide (324; R=H) (0.198 g., 66%), m.p. 117-119°; NMR and IR spectra were identical to those of (324; R=H) prepared by reduction of the keto-amide (319) by sodium borohydride.

The ice-cold solution A was basified with aqueous ammonia and extracted with ether (3 x 20 ml). The combined extracts were washed with water (20 ml), brine (20 ml), dried (Na_2SO_4) and evaporated to dryness to obtain a red gum (40 mg., 13% w/w), multicomponent by TLC. Attempted isolation of pure components by PLC was unsuccessful.

b) A similar reaction was carried out in boiling dioxan but only 15% w/w of basic material was isolated and this was also an intractable red gum.

N-(2,2-Dimethoxyethyl)-2,3-dimethoxy-6-[2-methoxy-2-(3,4-methylenedioxyphenyl)ethyl] benzamide (324; R=Me).

A solution of the hydroxy-amide (324; R=H) (2.53 g., 5.55 mmol) in methanol (40 ml) and acetic acid (40 ml) was heated under reflux for 2.5 hours, then evaporated to dryness. The residue was dissolved in chloroform (40 ml) and washed with 2N ammonia (20 ml), brine (2 x 20 ml), dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in warm benzene (ca. 50 ml) and petrol (60-80°, ca. 60 ml) was added until the solution became cloudy. After standing at 17° for 16 hours, the solid was collected and dried to recover (324; R=H) (1.23 g., 49%). The filtrate was evaporated to dryness and the residue

(~ 1.3 g.) was chromatographed (PLC, 1 metre plate, 1.0 mm. thickness) on alumina (Nagel), eluting 11 times (100% benzene), to obtain N-(2,2-dimethoxyethyl)-2,3-dimethoxy-6-[2-methoxy-2-(3,4-methylenedioxyphenyl)ethyl] benzamide (324; R=Me) (0.80 g., 1.79 mmol, 31%) as a colourless viscous gum; $\lambda_{max.}$(nm) (ε) (EtOH) 285 (6,750), $\lambda_{inflex.}$228 (14,900); $\nu_{max.}$($cm.^{-1}$) (thin film) 3300 (broad, NH), 2840 (w, OMe), 1660 (CO.NH), 935 (OCH_2O); NMR ($CDCl_3$) 2.82, 2.86, 2.92 and 3.00 (4 's'; $-NH\underline{CH_2}-$); 3.13 (3H, s; $ArCHO\underline{CH_3}$); 3.43 (6H, s; $CH(O\underline{CH_3})_2$); 3.58 (2H, 't', J = 5 Hz; $Ar\underline{CH_2}-$); 4.1-4.45 (1H, m; $CH_2\underline{CH}(OCH_3)_2$); 4.52 (1H, t, J = 5 Hz; $Ar\underline{CH}-OCH_3$); 5.97 (2H, s; $-OCH_2O-$); 6.3-6.7 (1H, broad; $-\underline{NH}$); 6.7-6.95 (5H, m; aromatics) (Found: C, 61.6; H, 6.4; N, 3.2. $C_{23}H_{29}NO_8$ requires C, 61.7; H, 6.5; N, 3.1%).

Attempted cyclizations of N-(2,2-dimethoxyethyl)-2,3-dimethoxy-6-[2-methoxy-2-(3,4-methylenedioxyphenyl)ethyl] benzamide (324; R=Me).

a) Compound (324; R=Me) (200 mg) was dissolved in benzene (10 ml) and triethylamine (10 ml) and the solution was heated under reflux for 3 hours. After cooling, the solution was evaporated to dryness to recover unchanged (324; R=Me) (197 mg).

b) Compound (324; R=Me) (200 mg) was added to a suspension of sodium hydride (26 mg., 50% oil suspension, 1.2 molar equivs.) in dry dimethylformamide (30 ml) under nitrogen. The mixture was stirred for 3 hours at ca. 50-60°, then n-propanol (5 ml) was added and the solution was evaporated to near dryness. The residual oil was shaken with ether (40 ml) and water (10 ml) and the ethereal solution was washed with water (2 x 10 ml), brine (20 ml) and dried (Na_2SO_4) and evaporated to dryness to recover crude starting material (324; R=Me) (204 mg.).

c) Compound (324; R=Me) (200 mg) was dissolved in hot tetralin (10 ml) and decalin (10 ml) and the solution was heated under reflux for 6 hours. Petrol (80-100°; 30 ml) was added to the cooled mixture and solvent was decanted to leave a gum which was washed with petrol (40-60°; 3 x 5 ml) and dried to recover starting material (324; R=Me) (173 mg).

Analyses of the above products were by means of NMR, IR and qualitative UV spectra, and TLC.

Attempted preparation of N-(2,2-dimethoxyethyl)-2,3-dimethoxy-6-[2-methoxy-2-(3,4-methylenedioxyphenyl)ethyl] benzylamine (327; R=H, R^1=OMe).

A 1M solution of diborane in diglyme (10 ml) was added to a solution of the methoxy-amide (324; R=Me) (0.280 g.) in diglyme (10 ml) and the solution was left at 21° for 12 hours, then heated under reflux for 5 hours. Methanol (5 ml) was added to the cooled solution and, after 10 minutes, the solution was evaporated to near dryness. Methanol (25 ml) and 2N sodium hydroxide (7.5 ml) were added and the solution was heated under reflux for 3.5 hours, then evaporated to near dryness. The residue was dissolved in ether (30 ml) and water (20 ml) and the ethereal solution was extracted with ice-cold 2N sulphuric acid (2 x 10 ml). The combined extracts were basified with aqueous ammonia and extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to dryness to obtain a light grey gum (0.197 g., 70% w/w); NMR ($CDCl_3$) (in part only) 3.1 to 3.5 (~ 2H, m).

2,3-Dimethoxy-6-iodobenzamide (329; R=H).

A solution of 2,3-dimethoxy-6-iodobenzoic acid (4.00 g., 13.0 mmol) in dichloromethane (50 ml) and thionyl chloride (5.0 ml) was heated under reflux for 4 hours, then evaporated to dryness. The residual oil was dissolved in dry benzene (40 ml) and the solution was evaporated to dryness and this process was repeated with further portions of dry benzene. The oil was dissolved in benzene (50 ml) and the solution was stirred with 36% ammonia solution (50 ml) for ten minutes. Petrol (60-80°, 100 ml) was added and the mixture was filtered. The yellow solid was washed thoroughly with water, then with ether (20 ml) and dried to give 2,3-dimethoxy-6-iodobenzamide (329; R=H) (3.76 g., 94%) as a pale yellow solid, m.p. 200-203°; $\lambda_{max.}$(nm) (ε) (EtOH) 236 (13,800), 284 (2,790); $\nu_{max.}$(cm.$^{-1}$) ($CHBr_3$) 3400 (sh, s), 3200 (sh, s), 1640 and 1610 (CO.NH); NMR ($CDCl_3$ + DMSO-d^6) 3.5-4.1 (1H, broad, removed by D_2O; -NH); 3.85 (6H, s, 2 x Ar-OCH_3); 6.77 (1H, d, J = 8.5 Hz; C_4-H); 7.51 (1H, d, J = 8.5 Hz; C_5-H); ~ 7.1 and ~ 7.5 (1H, "d", broad, removed by D_2O; -NH) (Found: C, 34.9; H, 3.1; N, 4.5; I, 40.8. $C_9H_{10}INO_3$ requires C, 35.2; H, 3.3; N, 4.6; I, 41.3%).

N-(2,2-Dimethoxyethyl)-2,3-dimethoxy-6-iodobenzamide [329; R=$CH_2CH(OMe)_2$].

A solution of 2,3-dimethoxy-6-iodobenzoic acid (2.00 g., 6.5 mmol) in dichloromethane (25 ml) and thionyl chloride (2.5 ml) was heated under reflux for 4 hours, then evaporated to dryness. The residual oil was evaporated to dryness with

several portions of dry benzene, then dissolved in benzene (25 ml) and pyridine (5 ml). Aminoacetal (5 ml) was added and the mixture was stirred for 2 hours, then diluted with ethyl acetate (50 ml), and washed with 2N hydrochloric acid (50 ml), water (50 ml), brine (50 ml) and dried (Na_2SO_4) and evaporated to dryness. The resultant viscous red oil (2.69 g.) was triturated with petrol (60-80°) and the solid was dried to give N-(2,2-dimethoxyethyl)-2,3-dimethoxy-6-iodobenzamide [329; R=$CH_2CH(OMe)_2$] (2.26 g., 85%), m.p. 87-89°; $\lambda_{max.}$(nm) (ε) (EtOH) 237 (13,500), 284 (3,280); $\nu_{max.}$($cm.^{-1}$) (nujol) 3350, 1660; NMR ($CDCl_3$) 3.42 [6H, s; $-CH(O\underline{CH_3})_2$]; 3.54 (2H, q, J = 6 Hz; $-NH\underline{CH_2}-$); 3.84 (6H, s; 2 x Ar-$O\underline{CH_3}$); 4.54 (1H, t, J = 6 Hz; $CH_2\underline{CH}-$); 6.0 (1H, broad s; $-CO.\underline{NH}-$); 6.67 (1H, 'd', J = 9 Hz; $C_4-\underline{H}$); 7.47 (1H, 'd', J = 9 Hz; $C_5-\underline{H}$) (Found: C, 39.3; H, 4.4; I, 32.3; N, 3.4. $C_{13}H_{18}INO_5$ requires C, 39.5; H , 4.6; I, 32.1; N, 3.5%).

3-(2,3-Dimethoxybenzylamino)-1-(3,4-methylenedioxyphenyl)but-2-enone (332).

A solution of 2,3-dimethoxybenzylamine (1.00 g., 6.00 mmol) and 1-(3,4-methylenedioxyphenyl)butan-1,3-dione (300) (1.30 g., 6.00 mmol) in toluene (100 ml) was heated under reflux, under a Dean and Stark water separator, for 16 hours. The solution was evaporated to dryness, triturated first with petrol (60-80°), then with ether, and the residual pale yellow solid was dried to obtain 3-(2,3-dimethoxybenzylamino)-1-(3,4-methylenedioxyphenyl)-but-2-enone (332) (1.08 g., 3.04 mmol, 51%) m.p. 131-132°.

$\lambda_{max.}$(cm.$^{-1}$) (nujol) 1600 (broad) $\lambda_{max.}$(nm) (ε) (EtOH) 228 (18,700), 274 (5,000), 350 (29,200); NMR ($CDCl_3$) 2.04 (3H, broad s; $\underline{CH_3}$-C=CH) (sharp after deuteration); 3.82 (3H, s; $\underline{CH_3}$-O); 3.85 (3H, s; $\underline{CH_3}$-O); 4.50 (2H, d, J = 6 Hz; Ar-$\underline{CH_2}$-N-); 5.61 (1H, s; CO-$\underline{CH}$=C-); (removed on deuteration); 5.91 (2H, s; -O$\underline{CH_2}$O-); 6.76 (1H, d, J = 7 Hz; C_5-$\underline{H}$ on aroyl group); 6.85-7.1 (3H, m; aromatics on benzyl group); 7.38 (1H, d, J = 1.5 Hz; C_2-$\underline{H}$ on aroyl group); 7.44 (1H, d of d, J = 7 Hz and 1.5 Hz; C_6-$\underline{H}$ on aroyl group); 7.3-7.6 (1H, broad, removed by D_2O; -$\underline{NH}$) (Found: C, 67.4; H, 6.0. $C_{20}H_{21}NO_5$ requires C, 67.6; H, 6.0%).

N-Benzyl acetoacetamide (338; R=$PhCH_2$).

A solution of benzylamine (2.14 g., 20 mmol) and ethyl acetoacetate (2.60 g., 20 mmol) in toluene (100 ml) was heated under reflux for 16 hours under a Dean and Stark water separator. The solution was evaporated to dryness and the residue was triturated with ether and dried to obtain N-benzyl acetoacetamide (338; R=$PhCH_2$) as a pale yellow solid (2.90 g., 76%), m.p. 94-95°, $\nu_{max.}$(nujol) (cm.$^{-1}$) 1600 (broad), $\lambda_{max.}$(nm) (ε) (EtOH) 247.5 (1,380), $\lambda_{inflex.}$256.5 (1,200), 263.5 (840), 267 (610); NMR ($CDCl_3$) 1.82 (10% of 3H, s; $\underline{CH_3}$-C(OH)=); 2.13 (90% of 3H, s; $\underline{CH_3}$CO-); 3.30 (90% of 2H, s, removed on deuteration; CO-$\underline{CH_2}$-CO); 4.36 (2H, d, J = 5 Hz, collapsing to s at 4.32 on deuteration; Ar-$\underline{CH_2}$-N<); 7.27 (5H, s; aromatics), 7.1-7.7 (1H, broad m, removed on deuteration; -$\underline{NH}$-) (Found: C, 68.9; H, 6.9. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.9%).

2,3-Dimethoxybenzaldoxime.

A solution of hydroxyammonium chloride (10.5 g., 0.15 mol) in water (12.5 ml) was added to a solution of 2,3-dimethoxybenzaldehyde (20.75 g., 0.125 mol) in warm ethanol (50 ml), followed by a solution of sodium hydroxide (7.5 g., 0.19 mol) in water (10 ml). The resultant white mixture was stood at 21° for 20 hours, then crushed ice (80 g.) was added. The mixture was saturated with carbon dioxide, filtered, and the residue was washed with water (3 x 30 ml), and dried to obtain 2,3-dimethoxybenzaldoxime (20.02 g., 89%), $\nu_{max.}$ ($cm.^{-1}$) (nujol) 3200 (OH), 1655 (-C=N-); NMR ($CDCl_3$) 3.87 (6H, s, 2 x -O$\underline{CH}_3$); 6.8-7.5 (3H, m; aromatics), 8.5 (s, 1H, Ar-$\underline{CH}$=N); 9.3 (1H, broad s, removed on deuteration; =N-$\underline{OH}$).

2,3-Dimethoxybenzylamine.

Zinc powder (50 g.) was added portionwise over 0.75 hours to a stirred solution of 2,3-dimethoxybenzaldoxime (32.3 g., 0.178 mol) in glacial acetic acid (200 ml) at 55 to 70°. After stirring for a further 0.75 hours, the mixture was filtered, the residue was washed with hot acetic acid, and the combined filtrates were evaporated to near dryness under reduced pressure. The residue was basified with aqueous ammonia and extracted with chloroform (1 x 150 ml, 2 x 50 ml). The combined extracts were then extracted with 2N. HCl (1 x 250 ml, 1 x 100 ml) and the combined aqueous acid extracts were basified with aqueous ammonia and extracted with chloroform (1 x 200 ml, 2 x 50 ml), washed with water, dried (Na_2SO_4) and

evaporated to dryness to obtain 2,3-dimethoxybenzylamine as a yellow oil (24.67 g., 83%). Treatment of an ethereal solution of 2,3-dimethoxybenzylamine with hydrogen chloride gas afforded 2,3-dimethoxybenzylammonium chloride as a white solid (quantitative conversion), m.p. 157-159°; $\lambda_{max.}$(nm) (ε) 278 (2,100); $\nu_{max.}$($cm.^{-1}$) 3200-2500 (br, mult.); 2010, 1970, 1900, 1800 (1,2,3-trisubstituted benzene) 805 (s), 768 (s), 738 (s), 700 (m); NMR (DMSO-d^6) 3.78 (6H, s; 2 x $O\underline{CH_3}$); 2.9 (2H, broad s; $Ar\underline{CH_2}$-NH_2^+); 6.95-7.2 (3H, m; aromatics); 8.3-9.0 (3H, broad, -$\underline{NH_3}^+$); after D_2O, 3.75 and 3.82 (6H, d; 2 x $O\underline{CH_3}$); 4.01 (2H, s; $Ar\underline{CH_2}$-NH_3^+); 7.10 (3H, s; aromatics) (Found: C, 52.8; H, 6.7; N, 6.6; Cl, 17.6. $C_9H_{14}ClNO_2$ requires C, 53.0; H, 6.9; N, 6.9; Cl, 17.4%).

3,4-Methylenedioxyphenacyl methylsulphoxide (349).

Sodium hydride (29.6 g., 50% oil suspension, 0.616 mol) was washed with petrol (40-60°) (3 x 200 ml) under nitrogen, then dry dimethylsulphoxide (600 ml) was added and the effervescent mixture was stirred at $\leq 68°$ for 2 hours to obtain a light grey solution. Dry tetrahydrofuran (300 ml) was added and the solution was cooled to ca. 6°. A solution of methyl 3,4-methylenedioxybenzoate (54.0 g., 0.300 mol) in in dry tetrahydrofuran (180 ml) was added with stirring over 10 minutes, temp. $\leq 15°$. The solution was stirred for 1.3 hours at 15°, poured into water (4 litres), acidified with conc. HCl (100 ml) and extracted with chloroform (4 x 500 ml). The combined extracts were washed with water (1 litre), dried (Na_2SO_4) and evaporated to small volume when a white solid

began to precipitate. The mixture was diluted with ether (1.3 litres), stood for 2 hours at 21°, filtered, washed with ether and dried to obtain 3,4-methylenedioxyphenacyl methylsulphoxide (349) (57.0 g., 84%) m.p. 112-113°, $\lambda_{max.}$(nm) (ε) (EtOH) 206 (14,100), 234 (16,100), 281 (6,550), 318 (8,820), $\lambda_{min.}$218 (6,810), 254 (1,640), 294 (4,790); $\nu_{max.}$($cm.^{-1}$) (nujol) 1665; NMR ($CDCl_3$) 2.71 (3H, s; O=S-$\underline{CH_3}$); 4.15 and 4.43 (2H, d of d, J = 14 Hz; -CO$\underline{CH_2}$-); 6.04 (2H, s; -O$\underline{CH_2}$O-); 6.85 (1H, d, J = 8 Hz; C_5-$\underline{H}$); 7.40 (1H, d, J = 2 Hz; C_2-$\underline{H}$); 7.56 (1H, d of d, J = 8 Hz and 2 Hz; C_6-$\underline{H}$) (Found: C, 53.1; H, 4.5; S, 13.8. $C_{10}H_{10}O_4S$ requires C, 53.1; H, 4.5; S, 14.1%).

ω,ω-Dimethoxy-3,4-methylenedioxyacetophenone (352).

A solution of 3,4-methylenedioxyphenacyl methylsulphoxide (348) (33.9 g., 150 mmol) and iodine (24 g., 94 mmol) in A.R. methanol (300 ml) was heated under reflux for 2 hours, then cooled, and evaporated to dryness. The residue was dissolved in dichloromethane (300 ml) and washed with aqueous sodium thiosulphate solution. The very pale yellow organic phase was washed with aqueous sodium bicarbonate, dried (K_2CO_3) and evaporated to dryness to obtain , -dimethoxy-3,4-methylenedioxyacetophenone (352) (32.10 g., 95.5%) as a pale yellow oil. Distillation of a sample (4.7 g.) afforded a pale yellow oil (3.0 g., 64% recovery), b.p. 112-116° (0.07 mm Hg), $\lambda_{max.}$ (nm) (ε) (EtOH) 232.5 (15,700) 277.5 (6,700), 314.5 (8,160); $\nu_{max.}$(thin film) 2825 (sharp), 1670 (C=O) 930 (-O$\underline{CH_2}$O-); NMR ($CDCl_3$) 3.44 (6H, s; 2 x -O$\underline{CH_3}$); 5.08 (1H, s; CO-$\underline{CH}$-); 6.00 (2H, s; -O$\underline{CH_2}$O-);

6.80 (1H, d, J = 8 Hz; C_5-H); 7.53 (1H, d, J = 1.5 Hz; C_2-H); 7.75 (1H, d of d; J = 8 Hz and 1.5 Hz; C_6-H) (Found: C, 59.1; H , 5.2. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%).

α-(2,3-Dimethoxybenzylamino)-3,4-methylenedioxyphenylacetaldehyde dimethylacetal (341).

A solution containing 2,3-dimethoxybenzylamine (28.3 g., 169 mmol), ω ,ω-dimethoxy-3,4-methylenedioxyacetophenone (35.0 g., 156 mmol) and p-toluenesulphonic acid (0.1 g.) in toluene (500 ml) was heated under reflux for 24 hours under a Dean and Stark head. The light red solution was evaporated to dryness and the residue was dissolved in methanol (500 ml), cooled to ca. 5° using an ice-bath, and sodium borohydride (20 g.) was added in portions over 20 minutes with stirring. The solution was stirred at 21° for 1.5 hours then evaporated to near dryness. The residue was shaken with ether and water and the ice-cold ethereal solution was extracted with ice-cold 2N sulphuric acid (1 x 150 ml, 3 x 50 ml). The combined acid extracts were basified with aqueous ammonia (d 0.88) with ice-cooling, extracted with ether (1 x 300 ml, 2 x 100 ml) and the combined ethereal solutions were washed with water (200 ml), brine (2 x 200 ml), dried (Na_2SO_4) and evaporated to dryness. The resultant light red oil (44 g.) was chromatographed on neutral alumina (2.5 kg.), eluting with 33% chloroform in petrol (60-80°). The first 3 litres of eluate were discarded and the following 9 litres (monitoring by TLC) were evaporated to dryness. The resultant oil was dissolved in ether, ice-cooled, and

extracted with ice-cold 2N sulphuric acid. The aqueous acid solution was basified with aqueous ammonia (d 0.88) with cooling and extracted with ether. The ethereal extract was washed with water, brine, dried (Na_2SO_4) and evaporated to dryness to obtain <u>α-(2,3-dimethoxybenzylamino)-3,4-methylenedioxyphenylacetaldehyde dimethylacetal (341)</u> (20.8 g., 55.8 mmol, 36%) as a viscous pale yellow oil, $\lambda_{max.}$(nm) (ε) (EtOH) 281 (5,070) $\lambda_{inflex.}$239.5 (4,880) 287 (4,540) $\nu_{max.}$($cm.^{-1}$) (thin film) 3400 (NH) 2850 (OCH_3) 935 (OCH_2O); NMR ($CDCl_3$) 2.7 (1H, broad s; -<u>NH</u>); 3.13, 3.23, 3.29, 3.40 (6H, singlets; 2 x CHO<u>CH_3</u>); 3.54 (1H, d, J = 5.5 Hz; ½ of Ar-<u>CH_2</u>-N-); 3.7-3.9 (7.5 H, m; 2 x Ar<u>OCH_3</u>, ½ of Ar-<u>CH_2</u>-N, ½ of Ar-<u>CH</u>-CH-); 4.22 (0.5 H, d, J = 7.0 Hz, ½ of CH_3O-<u>CH</u>-OCH_3); 4.48 (0.5 H, d, J = 6.3 Hz; ½ of CH_3O<u>CH</u>OCH_3) 5.87 (2H, s, -O<u>CH_2</u>O-); 6.6-7.1 (6H, m; aromatics) (Found: C, 63.7; H, 6.5; N, 3.7. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%).

<u>N-Methyl-N-(2,3-dimethoxybenzyl)- -amino-(3,4-methylenedioxy-phenylacetaldehyde dimethyl acetal (364).</u>

A solution of the amine (341) (0.500 g., 1.33 mmol), aqueous formaldehyde (37%, 5 ml) and formic acid (98%, 5 ml) was heated on a steam bath for 1.5 hours, cooled, basified with aqueous ammonia and extracted with ether (1 x 40 ml, 2 x 10 ml). The combined ethereal extracts were washed with water (1 x 40 ml), ice-cooled, and extracted with ice cold 2N HCl (3 x 10 ml). The combined acid extracts were basified with aqueous ammonia and extracted with ether (1 x 40 ml, 2 x 10 ml). The combined extracts

were washed with water (2 x 20 ml), brine (2 x 20 ml), dried (Na_2SO_4) and evaporated to dryness to afford N-methyl-N-(2,3-dimethoxybenzyl)-α-amino-(3,4-methylenedioxyphenylacetaldehyde dimethyl acetal (364) as a pale yellow viscous oil (0.500 g., 96%) $\lambda_{max.}$ (nm) (ε) (EtOH) 281 (5,020) $\lambda_{inflex.}$ 240 (5,720) 286 (4,550); $\nu_{max.}$ ($cm.^{-1}$) (thin film) 2850 (OCH_3) 935 (OCH_2O); NMR ($CDCl_3$) 2.19 and 2.22 (3H, singlets, N-CH_3); 3.30 (s, 3H, CH_3O-CH-OCH_3); 3.44 and 3.48 (3H, singlets, CH_3O-CH-OCH_3); 3.59 ($\frac{3}{4}$ of 2H, broad s, ArCH_2-N<); 3.64 ($\frac{1}{4}$ of 2H, broad s, ArCH_2-N<); 3.75 (1H, d, J = 6.7 Hz, ArCH-$CH(OCH_3)_2$); 3.79, 3.83 and 3.85 (6H, singlets, 2 x ArOCH_3); 5.95 (2H, s, -O-CH_2-O); 6.7 to 7.2 (6H, m, aromatics) (Found: C, 64.8; H, 6.7; N, 3.5. $C_{21}H_{27}NO_6$ requires C, 64.7; H, 7.0; N, 3.6%).

7,8-Dimethoxy-4-hydroxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (367).

A solution of α-(2,3-dimethoxybenzylamino)-3,4-methylenedioxyphenylacetaldehyde dimethyl acetal (4.20 g., 11.2 mmol) in methanol (100 ml) was cooled in an ice bath and 36% hydrochloric acid (100 ml, A.R.) was added and the light red solution was kept at room temperature for 2 days. The solution was evaporated to small bulk under reduced pressure, temperature $\not>$ 40°, and filtered. The solid was washed with a small amount of water and shaken with 2N ammonia (50 ml) and chloroform (50 ml). The organic phase was washed with water (50 ml), brine (50 ml), dried (Na_2SO_4) and evaporated to dryness. The resultant off-white solid (0.620 g.) was triturated with ether and dried to afford 7,8-dimethoxy-4-hydroxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-

isoquinoline (367) as a white solid (0.600 g., 16.3%), m.p. 162-164°, $\lambda_{max.}$ (nm) (ϵ) (EtOH) 205 (58,000) 283 (6,170), $\lambda_{min.}$ 257 (1,510), $\lambda_{inflex.}$ 231 (14,600); $\nu_{max.}$ ($cm.^{-1}$) ($CHBr_3$) 3530 (OH) 3200 (NH) 930 (OCH_2O), no change in absorption positions above 3000 $cm.^{-1}$ on dilution; NMR ($CDCl_3$) 2.32 (2H, s, removed on deuteration; -OH and -NH); 3.8-3.9 (7H, s; 2 x $ArOCH_3$ and $ArCH-CHOH$); 3.92 (1H, d, J = 15 Hz; $ArCH(H)-NH-$); 4.32 (1H, d, J = 15 Hz; $ArCH(H)-NH-$); 4.49 (1H, s; $ArCH-OH$); 5.91 (2H, s; $-OCH_2O-$); 6.75-7.24 (5H, m; aromatics) (Found: C, 65.7; H, 4.3. $C_{18}H_{19}NO_5$ requires C, 65.6; H, 4.3%).

α-Cyano-N,N-diethyl-3,4-methylenedioxybenzylamine (388).

A solution of piperonal (32.9 g., 0.219 mol) in methanol (130 ml) was added to a solution of diethylammonium chloride (31.9 g., 0.33 mol) and sodium cyanide (24 g., 0.49 mol) in water (150 ml) and stirred for 18 hours at 19°. The pale red two-phase solution was diluted with water (800 ml) and extracted with ether (1 x 500 ml, 1 x 150 ml) and the combined ethereal extracts were washed with aqueous sodium metabisulphite (6 x 150 ml), water (150 ml), brine (2 x 150 ml) and dried ($MgSO_4$). Evaporation of the ethereal solution gave α-cyano-N,N-diethyl-3,4-methylenedioxybenzylamine (388) as a red oil (41.25 g., 81%); NMR ($CDCl_3$) 1.07 (6H, t; J = 7.5 Hz; 2 x CH_2CH_3); 2.53 (2H, q, J = 7.5 Hz; CH_2CH_3); 2.61 (2H, q, J = 7.5 Hz; CH_2CH_3); 4.92 (1H, s; CH-CN); 5.99 (2H, s; $-OCH_2O-$); 6.80 (1H, d; J = 8 Hz; C_5-H); 7.02 (1H, s; C_2-H), 7.06 (1H, d; J = 8 Hz, C_6-H) (Found: C, 65.3; H, 7.0; N, 11.6. $C_{12}H_{16}N_2O_2$ requires C, 65.5; H, 7.3; N, 12.7%).

N,N-Diethyl-1-cyano-2-(3,4-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (392).

Sodium hydride (0.66 g., 60% suspension in oil, 16.5 mmol) was washed with petrol (40-60°) under nitrogen then dry dimethylformamide (50 ml) was added, followed by N,N-diethyl-α-cyano-3,4-methylenedioxybenzylamine (388) (3.48 g., 15.0 mmol). After stirring for 2.5 hours, 3,4-dimethoxybenzyl chloride (2.90 g., 15.5 mmol) was added and the mixture was stirred at room temperature for 16 hours, then evaporated to near dryness. The resultant red oil was stirred for 2 hours in dichloromethane (100 ml) and 2N hydrochloric acid (100 ml). The organic phase was washed with aqueous sodium bicarbonate solution (50 ml), water (50 ml), dried ($MgSO_4$) and evaporated to dryness. The resultant yellow semi-solid (4.80 g.) was triturated with ether and the residue was dried to give N,N-diethyl-1-cyano-2-(3,4-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (392) (1.61 g., 28%), m.p. 127-129°, $\nu_{max.}$ (cm.$^{-1}$) ($CHBr_3$) 2850 (OCH_3), 2795 (w) 945 (OCH_2O), NMR ($CDCl_3$) 1.14 (6H, t, J = 7.5 Hz, 2 x $-CH_2\underline{CH_3}$); 2.77 (2H, q, J = 7.5 Hz; $-\underline{CH_2}CH_3$); 2.80 (2H, q, J = 7.5 Hz, $-\underline{CH_2}CH_3$); 2.82 [1H, d, J = 13 Hz; Ar-$\underline{CH}$(H)-]; 3.49 [1H, d, J = 13 Hz; Ar-CH($\underline{H}$)-]; 3.63 (3H, s, Ar-$O\underline{CH_3}$); 3.80 (3H, s, Ar-$O\underline{CH_3}$); 5.93 (2H, s; $-O\underline{CH_2}O-$); 6.17 (1H, d, J = 2 Hz, C_2-$\underline{H}$ on veratryl); 6.47 (1H, d of d, J = 2 Hz and 8.5 Hz; C_6-$\underline{H}$ on veratryl); 6.70 (1H, d, J = 8.5 Hz; C_5-$\underline{H}$ on veratryl); 6.75-6.95 (2H, m; C_2-$\underline{H}$ and C_5-$\underline{H}$ on piperonyl); 7.0 (1H, m, C_6-$\underline{H}$ on piperonyl) (Found: C, 68.9; H, 6.85; N, 7.5. $C_{22}H_{26}N_2O_4$ requires C, 69.1; H, 6.85; N, 7.3%).

3,4-Dimethoxybenzyl-3,4-methylenedioxyphenyl ketone (391; R=Me).

A solution of N,N-diethyl-1-cyano-2-(3,4-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (392) (0.383 g., 1.00 mmol) in dichloromethane (50 ml) was stirred with 2N hydrochloric acid for 2 days. The organic phase was washed with water (2 x 50 ml), brine (50 ml), dried (Na_2SO_4) and evaporated to dryness. The off-white solid was crystallized from ethanol to afford 3,4-dimethoxybenzyl-3,4-methylenedioxyphenyl ketone (0.240 g., 80%), m.p. 110-111° (lit.[253] 110-111°) $\nu_{max.}$(cm.$^{-1}$) ($CHBr_3$) 1670 (Found: C, 68.2; H, 5.4. Calcd. for $C_{17}H_{16}O_5$ C, 68.0; H, 5.4%).

3,4-Methylenedioxyphenyl (2-nitro-4,5-methylenedioxybenzyl) ketone

Sodium hydride (0.400 g., 60% dispersion in oil, 10 mmol) was washed with petrol (40-60°) under nitrogen, then dry dimethylformamide (40 ml) was added, followed by α-cyano-N,N-diethyl-3,4-methylenedioxybenzylamine (388) (2.32 g., 10 mmol). After stirring for 3 hours at 21°, 2-nitro-4,5-methylenedioxybenzyl chloride (390) (1.32 g., 6.1 mmol) was added, followed by dimethylformamide (10 ml). The mixture was stirred for 20 hours at 21°, then 2N hydrochloric acid (80 ml) was added and the solution was stirred for 2 hours. Water (300 ml) was added and the mixture was extracted with dichloromethane (200 ml, 3 x 50 ml). The combined extracts were washed with water (100 ml), brine (100 ml), dried ($MgSO_4$), and evaporated to dryness. The dark red semi-solid gum was triturated with ether and the light brown solid obtained was dried (1.17 g.) and crystallized from methanol to give 3,4-methylenedioxyphenyl (2-nitro-4,5-methylenedioxybenzyl)ketone

(1.01 g., 48%) as yellow needles, m.p. 171-172°, $\lambda_{max.}$(nm) (ε) (EtOH) 203 (21,200), 230 (19,300), 275 (8,000), 313 (9,900) $\lambda_{min.}$215 (13,200), 263 (7,100), 288 (6,400), $\lambda_{inflex.}$252 (9,400), 345 (5,200); $\nu_{max.}$($cm.^{-1}$) ($CHBr_3$) 1670 (C=O), 940 (OCH_2O); NMR (DMSO-d^6) 3.71 (2H, s, Ar$\underline{CH_2}$CO); 6.18 (2H, s; -O$\underline{CH_2}$O- on piperonoyl), 6.28 (2H, s;-OCH_2O- on nitropiperonyl); 7.08 (1H, d, J = 8 Hz; C_5-$\underline{H}$ on piperonoyl); 7.11 (1H, s; C_2-$\underline{H}$ on nitropiperonyl); 7.52 (1H, d, J = 1.5 Hz; C_1-$\underline{H}$ on piperonoyl); 7.71 (1H, s, C_2-$\underline{H}$ on nitropiperonyl), 7.73 (1H, d of d, J = 8 Hz and 1.5 Hz; C_6-$\underline{H}$ on piperonoyl) (Found: C, 58.3; H, 3.5; N, 4.2. $C_{16}H_{11}NO_7$ requires C, 58.4; H, 3.4; N, 4.2%).

<u>3-Benzyloxy-4-methoxybenzyl 3,4-methylenedioxyphenyl ketone (391; R=$PhCH_2$)</u>.

Sodium hydride (7.5 g., 60% suspension in oil, 0.187 mol) was washed with petrol (30-40°) under N_2 then a solution of α-cyano-N,N-diethyl-3,4-methylenedioxybenzylamine (388) (41.2 g., 0.177 mol) in dimethylformamide (200 ml) was added. The resultant red-brown suspension was stirred under nitrogen for 3 hours at 23° and 3-benzyloxy-4-methoxybenzyl chloride (38.3 g., 0.146 mol) was added and the mixture was stirred for a further 16 hours. The solvent was removed by evaporation under reduced pressure and the residue was stirred with dichloromethane (400 ml) and 1N sulphuric acid (400 ml) for 20 hours. The aqueous phase was extracted with more dichloromethane (100 ml) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 200 ml), brine (2 x 200 ml) and dried ($MgSO_4$).

Evaporation afforded a red oil, which, on trituration with ether, gave 3-benzyloxy-4-methoxybenzyl 3,4-methylenedioxyphenyl ketone (391; R=$PhCH_2$) (24.68 g., 45%) m.p. 110°, analytical sample (EtOH or trituration with ether) m.p. 113°, $\lambda_{max.}$(nm) (ε) (EtOH) 204 (66,400) 230 (29,800) 280 (8,800) 315 (8,500); $\nu_{max.}$($cm.^{-1}$) ($CHBr_3$) 2840 (OCH_3), 2785 (~), 1670 (C=O), 940 (OCH_2O); NMR ($CDCl_3$) 3.80 (3H, s; $ArOCH_3$); 4.02 (2H, s; $COCH_2Ar$); 5.08 (2H, s; $Ph-CH_2-O$); 5.95 (2H, s; $-OCH_2O-$); 6.78 (1H, d, J = 10 Hz; C_5-H on piperonoyl); 6.82 (3H, s; aromatics on dialkoxybenzyl); 7.2-7.5 (5H, m; $C_6H_5-CH_2-$); 7.35 (1H, d, J = 2 Hz; C_2-H on piperonoyl); 7.53 (1H, d of d, J = 2 Hz and 10 Hz; C_6-H on piperonoyl) (Found: C, 73.7; H, 5.5. $C_{23}H_{20}O_5$ requires C, 73.4; H, 5.4%).

N-(2,2-Dimethoxyethyl)-2-(3-benzyloxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (396; R=$PhCH_2$-).

A solution of 3-benzyloxy-4-methoxybenzyl 3,4-methylenedioxyphenyl ketone (391; R=$PhCH_2$-) (18.1 g., 48.2 mmol), p-toluenesulphonic acid (ca. 60 mg.) and aminoacetal (30 ml) in toluene (250 ml) was heated under reflux under a Dean and Stark head for 20 hours. Evaporation of the solvent gave a pale red oil which was dissolved in ethanol (350 ml) and treated with sodium borohydride (12 g.) with stirring. After 1.5 hours the solution was evaporated to near dryness and the residue was shaken with ether (400 ml) and water (400 ml). The ethereal solution was cooled by addition of ice and extracted with ice-cold 2N hydrochloric acid (3 x 50 ml). The combined extracts were basified with aqueous ammonia (d 0.88) and extracted with 10% chloroform in ether

(1 x 200 ml, 2 x 100 ml). The combined extracts were washed with water (100 ml), brine (100 ml), dried ($MgSO_4$) and evaporated to dryness. The resultant pale red oil was extracted with hot petrol (80-100°, 400 ml, 2 x 100 ml) and the extracts were combined, cooled to about 25°, and decanted from a trace of yellow oil. The colourless solution was kept at 4° for 20 hours, filtered, and the residue was dried to give N-(2,2-dimethoxyethyl)-2-(3-benzyloxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (396; R=$PhCH_2$-) (9.82 g., 44%) m.p. 65-66°, $\lambda_{max.}$(nm) (ε) (EtOH) 205 (86,900), 286 (6,300), $\lambda_{min.}$258 (900), $\lambda_{inflex.}$232 (17,900); $\nu_{max.}$($CHBr_3$) 3220 (NH), 2850 (OCH_3), 2790 (w), 940 (OCH_2O); NMR ($CDCl_3$) 2.0 (1H, broad s, removed by deuteration; -NH); 2.50 (2H, d, J = 5.5 Hz; CH_2NH); 2.76 (2H, d, J = 7 Hz; $ArCH_2CH$); 3.25 (6H, s; 2 x CH-O-CH_3); 3.65 (1H, t, J = 7 Hz; $ArCH-CH_2$); 3.82 (3H, s; Ar-OCH_3); 4.34 (1H, t, J = 5.5 Hz; CH_2CHOCH_3); 5.07 (2H, s; $PhCH_2$-); 5.92 (2H, s; -OCH_2O-); 6.6-7.0 (6H, m; aromatics); 7.3-7.5 (5H, m; C_6H_5-CH_2) (Found: C, 69.9; H, 6.7; N, 3.1. $C_{27}H_{31}NO_6$ requires C, 69.7; H, 6.7; N, 3.0%).

N-(2,2-Dimethoxyethyl)-2-(3-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (396; R=H).

Hydrogenolysis of N-(2,2-dimethoxyethyl)-2-(3-benzyloxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (396; R=$PhCH_2$-) (9.82 g., 21.1 mmol) in ethanol (300 ml) containing 10% palladium on charcoal (0.40 g.) at atmospheric pressure and crystallization from petrol (80-100°) gave N-(2,2-dimethoxyethyl-2-(3-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (396; R=H) (6.89 g., 87%) m.p. 85-86°, $\lambda_{max.}$(nm) (ε) (EtOH) 232 (11,300) 284.5

(8,030), $\lambda_{inflex.}$ 287 (7,800); $\nu_{max.}$ ($CHBr_3$) 3520 (OH, strong), 3300 (NH, weak), 2840 (OCH_3), 2780 (w), 940 (OCH_2O); NMR ($CDCl_3$) 2.51 (2H, d, J = 5.5 Hz; $-NH\underline{CH_2}-$); 2.7 (2H, m; $Ar\underline{CH_2}\overset{|}{C}H-$); 3.22 (6H, s; 2 x $-\overset{|}{C}HO\underline{CH_3}$); 3.6 (1H, m; $Ar\underline{C}HNH$); 3.80 (3H, s; $Ar-O\underline{CH_3}$); 3.90 (2H, s, removed on deuteration; $-O\underline{H}$ and $-N\underline{H}$); 4.37 (1H, t, J = 5.5 Hz; $CH_2\underline{C}\overset{|}{H}-OCH_3$); 5.90 (2H, s; $-O\underline{CH_2}O-$); 6.6-7.0 (6H, m; aromatics) (Found: C, 64.2; H, 6.7; N, 3.8. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%).

N-(2,2-Dimethoxyethyl)-8-hydroxy-7-methoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (406; R=OH, R^1=H).

A solution of N-(2,2-dimethoxyethyl)-2-(3-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (396; R=H) (3.01 g., 8.03 mmol) in methanol (60 ml) and 36% aqueous formaldehyde (25 ml) was stood at 21° for 5 hours, then at 4° for 20 hours. The solution was evaporated to near dryness and the residue was shaken with water and ether. The ethereal solution was ice-cooled and extracted with ice-cold 1N hydrochloric acid (2 x 60 ml). The combined acid extracts were basified by addition of solid sodium bicarbonate and the mixture was extracted with ether (3 x 100 ml). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and evaporated to dryness to afford a pale yellow-green oil (2.56 g.). Separation of the two major components was achieved by Preparative Layer Chromatography on alumina (Merck) with two elutions using 50% chloroform in petrol (60-80°). Fraction A, (TLC R_f 0.53, alumina, chloroform) was N-(2,2-dimethoxyethyl)-8-hydroxy-7-methoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (406; R=OH, R^1=H) (0.85 g., 27%). The hydrochloride

salt was obtained in ether and crystallized from water, m.p. 195-196° (decomp.), $\lambda_{max.}$ (nm) (ε) (EtOH) 205 (63,000), 233 (19,900), 286 (8,800), $\lambda_{min.}$ 229 (12,400), 257 (1,550); $\nu_{max.}$ ($cm.^{-1}$) ($CHBr_3$) 3290 (OH), 2490, 2440, 2380 (NH^+); NMR (free base) ($CDCl_3$) 2.46 and 2.63 (2H, doublets, J = 5 Hz; $-N\underline{CH_2}\overset{|}{C}H-$); 2.95 (2H, broad d, J ~ 7 Hz; $C_4-\underline{H}$); 3.28 (3H, s; $-\overset{|}{C}H-O\underline{CH_3}$); 3.31 (3H, s; $-\overset{|}{C}HO\underline{CH_3}$); 3.73 (1H, broad s, removed on deuteration; Ar-$\underline{OH}$); 3.3-4.15 (2H, m; $\underline{CH_2}$ at C_1); 4.3-4.7 (2H, m; $-N-\underline{\overset{|}{C}H}-Ar$ and $CH_2\underline{\overset{|}{C}H}-OCH_3$); 5.91 (2H, s; $-OCH_2O-$); 6.62 (1H, s, $C_5-\underline{H}$); 6.68 (1H, s; $C_6-\underline{H}$); 6.73-6.80 (2H, m; $C_2'-\underline{H}$ and $C_5'-\underline{H}$); 6.90 (1H, m, $C_6'-\underline{H}$) (Found: C, 59.1; H, 6.1; N, 3.2. $C_{21}H_{25}NO_6.HCl$ requires C, 59.5; H, 6.2; N, 3.3%).

Fraction B, an oil, (TLC R_f 0.47, alumina, chloroform) was <u>N-(2,2-dimethoxyethyl)-6-hydroxy-7-methoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (406; R=H, R^1=OH)</u> (1.15 g., 37%). The hydrochloride salt was obtained in ether and crystallized from water, m.p. 204-207°, $\lambda_{max.}$ (nm) (ε) (EtOH) 205 (61,400), 291 (7,500), $\lambda_{min.}$ 257 (720), $\lambda_{inflex.}$ 233 (9,800); $\nu_{max.}$ ($cm.^{-1}$) ($CHBr_3$) 3520 (OH), 2840 (OCH_3), 2520 (NH^+), 940 (OCH_2O); NMR (free base) ($CDCl_3$) 2.35 to 2.75 (2H, m, $-N-\underline{CH_2}-\overset{|}{C}H-$); 2.90 (2H, broad 'd', J ~ 7 Hz; $Ar\underline{CH_2}CH$); 3.28 3H, s; $-\overset{|}{C}H-O\underline{CH_3}$); 3.31 (3H, s; $-\overset{|}{C}H-O\underline{CH_3}$); 3.3-4.0 (2H, m; $Ar\underline{CH_2}\overset{|}{N}-$); 3.83 (3H, s, Ar-$O\underline{CH_3}$); 4.2-4.7 (2H, m; $ArCH_2\underline{\overset{|}{C}H}Ar$ and and $-CH_2\underline{\overset{|}{C}H}OCH_3$); 4.60 (1H, s, removed on deuteration; Ar-$\underline{OH}$); 5.93 (2H, s; $-O\underline{CH_2}O-$); 6.54 (1H, s; $C_8-\underline{H}$); 6.64 (1H, s, $C_5-\underline{H}$); 6.60-6.83 (2H, m; $C_2'-\underline{H}$ and $C_5'-\underline{H}$); 6.88-6.92 (1H, m; $C_6'-H$)

(Found: C, 58.3; H, 6.2; N, 3.2. $C_{21}H_{25}NO_6.HCl.\ \frac{1}{2}H_2O$ requires C, 58.3; H, 6.1; N, 3.2%).

N-(2,2-dimethoxyethyl)-6-hydroxy-7-methoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (406; R=H, R^1=OH).

A solution of N-(2,2-dimethoxyethyl)-2-(3-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethylamine (396; R=H) (0.518 g., 1.38 mmol) in methanol (12 ml), formic acid (98-100%, 8 ml) and 37% formaldehyde (6 ml) was stood at 21° for 5 hours, then at 4° for 22 hours, and evaporated to near dryness. The residue was shaken with ether (50 ml) and aqueous sodium bicarbonate (50 ml) and the ethereal solution was washed with water, cooled with ice, and extracted with ice-cold 1N hydrochloric acid (2 x 30 ml). The combined acid extracts were basified with solid sodium bicarbonate and the mixture was extracted with dichloromethane (3 x 20 ml). The combined extracts were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$) and evaporated to dryness. Trituration of the oil with ice-cold 0.5N hydrochloric acid (5 ml) gave an off-white solid which was crystallized from water to afford N-(2,2-dimethoxyethyl)-6-hydroxy-7-methoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (406; R=H, R^1=OH) (0.402 g., 67%), m.p. 204-207°, mixed m.p., with sample obtained by chromatographic separation, 204-207°. Both NMR and IR spectra were superimposable with those of sample obtained by chromatography (Found: C, 58.2; H, 6.2; N, 3.2. Calcd. for $C_{21}H_{25}NO_6.HCl.\ \frac{1}{2}H_2O$ C, 58.3; H, 6.1; N, 3.2%).

N-(2,2-Dimethoxyethyl)-7,8-dimethoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (406; R=OMe, R^1=H).

A solution of N-(2,2-dimethoxyethyl)-8-hydroxy-7-methoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (406; R=OH, R^1=H) (0.679 g., 1.75 mmol) in ether (100 ml) was added to a solution of diazomethane (~ 3 g.) in ether (120 ml) and the solution was stood for 3 days at room temperature. The solution was concentrated to $\frac{1}{4}$ volume, washed with water (20 ml) and extracted with 1N sodium hydroxide (2 x 20 ml), then with water (20 ml). The combined aqueous extracts were treated with gaseous carbon dioxide to obtain a milky suspension, which was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were washed with water (20 ml), brine (20 ml), dried ($MgSO_4$) and evaporated to dryness to recover (406; R=OH, R^1=H) (0.273 g., 39%). The ethereal solution was ice-cooled and extracted with ice-cold 1N hydrochloric acid (3 x 12 ml) and the combined aqueous acid extracts were basified with aqueous ammonia (d 0.88) and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were washed with water (20 ml), brine (20 ml), dried ($MgSO_4$), and evaporated to dryness to afford an oil (0.384 g.). The oil was extracted with hot cyclohexane and decanted from a trace of dark red-brown tar. The cooled cyclohexane solution was treated with hydrogen chloride gas then degassed with nitrogen and filtered. The residue was washed with dry ether and crystallized from water to obtain 2-(2,2-dimethoxyethyl)-7,8-dimethoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (406; R=OMe, R^1=H) (0.347 g., 45% conversion,

74% yield), m.p. 130-132°, $\lambda_{max.}$(nm) (ϵ) (EtOH) 205 (62,000), 289 (10,500), $\lambda_{min.}$257 (150), $\lambda_{inflex.}$233 (10,900); $\nu_{max.}$ ($cm.^{-1}$) ($CHBr_3$) 2850 (OCH_3), 2800 (w), 2500-2000 (NH^+), 940 (OCH_2O); NMR (free base) ($CDCl_3$) 2.48 and 2.67 (2H, doublets, J = 5 Hz; -$N\underline{CH_2}\underline{CH}$-); 2.98 (2H, broad d, J ~ 7 Hz; Ar$\underline{CH_2}\underline{CH}$Ar); 3.28 (3H, s; -$\underline{CH}$-$O\underline{CH_3}$); 3.32 (3H, s; $\underline{CH}O\underline{CH_3}$); 3.45-4.0 (2H, m; Ar$\underline{CH_2}$N-); 3.86 (6H, s, 2 x Ar-$O\underline{CH_3}$); 4.1-4.7 (2H, m; Ar-$\underline{CH}$-N- and CH_2-$\underline{CH}$-OCH_3); 5.95 (2H, s; -$O\underline{CH_2}O$-); 6.6-7.0 (5H, m; aromatics) (Found: C, 59.0; H, 6.5; N, 3.1. $C_{22}H_{28}ClNO_6.\frac{1}{2}H_2O$ requires C, 59.1; H, 6.5; N, 3.1%).

Similarly was prepared:-

<u>N-(2,2-Dimethoxyethyl)-6,7-dimethoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (406; R=H, R^1=OMe)</u>, 81% conversion, 92% yield, m.p. 159-160° (aqueous n-propanol), $\lambda_{max.}$(nm) (ϵ) (EtOH) 206 (61,500), 290 (10,000), $\lambda_{min.}$257 (0), $\lambda_{inflex.}$233 (10,000); $\nu_{max.}$($cm.^{-1}$) ($CHBr_3$) 2850 (OCH_3) 2790 (w), 2500-2000 (NH^+), 940 (OCH_2O); NMR (free base) ($CDCl_3$) 2.44 and 2.62 (2H, doublets, J = 5.5 Hz; -N-$\underline{CH_2}$-$\underline{CH}$-); 2.94 (2H, broad d, J ~ 7 Hz; Ar$\underline{CH_2}\underline{CH}$Ar); 3.26 (3H, s; -$\underline{CH}O\underline{CH_3}$); 3.31 (3H, s; -$\underline{CH}O\underline{CH_3}$); 3.5-3.9 (2H, m; Ar-$\underline{CH_2}$-N-); 3.93 (6H, s; 2 x Ar-$O\underline{CH_3}$); 3.95-4.30 (1H, m; Ar$\underline{CH}$-CH_2-); 4.49 (1H, t, J = 5 Hz; $CH_2\underline{CH}$-OCH_3); 5.93 (2H, s; -$O\underline{CH_2}O$-); 6.60 (2H, broad s; C_5-$\underline{H}$ and C_8-$\underline{H}$); 6.70 (2H, broad s; C_2'-$\underline{H}$ and C_5'-$\underline{H}$); 6.81 (1H, m; C_6'-$\underline{H}$) (Found: C, 57.0; H, 6.7; N, 3.0. $C_{22}H_{27}NO_6.HCl.\ 1\frac{1}{2}H_2O$ requires C, 56.8; H, 6.7; N, 3.0%).

Tetrahydroberberastine hydrochloride (408).

N-(2,2-Dimethoxyethyl)-7,8-dimethoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (406; R=OMe, R^1=H) (203 mg., 0.454 mmol) was dissolved in 6N hydrochloric acid (5 ml) and kept at 32° for 18 hours. The mixture was filtered and the residue was washed with water (2 x 2 ml) and dried to afford tetrahydroberberastine hydrochloride (408) (127 mg., 71%) as an off-white solid, m.p. 202-203°, $\lambda_{max.}$(nm) (ε) (EtOH) 205 (62,600), 287 (5,700), $\lambda_{min.}$260 (1,640), $\lambda_{inflex.}$231 (15,500); $\nu_{max.}$ ($cm.^{-1}$) ($CHBr_3$) 3550 (broad, OH), 2850 (OCH_3), 2780 (w), 2900-2700 (m, NH^+), 945 (OCH_2O); NMR (DMSO-d^6) 2.9-4.0 (8H, m; -NH, -OH, CH_2 at C-6, CH_2 at C-8, CH_2 at C-13); 3.79 (3H, s; $ArOCH_3$); 3.80 (3H, s; $ArOCH_3$); 4.4-4.9 (2H, m; C_5-H and C_{13}-H); 6.02 (2H, s; $-OCH_2O-$); 6.9-7.15 (4H, m; aromatics) (Found: C, 61.2; H, 5.8; N, 3.4. $C_{20}H_{21}NO_5.HCl$. requires C, 61.3; H, 5.7; N, 3.6%).

5-Ethoxy-8,9-dimethoxy-2,3-methylenedioxyberbine (412).

N-(2,2-Dimethoxyethyl)-7,8-dimethoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (406; R=OMe, R^1=H) (203 mg., 0.454 mmol) was dissolved in ethanol (7.0 ml) and 36% hydrochloric acid (7.0 ml) and kept at 38° for 12 hours, then at 21° for 10 hours. The mixture was evaporated to near dryness at $\not>$40°, and 2N sodium hydroxide was added and extracted repeatedly with chloroform. The combined extracts (50 ml) were washed with water (2 x 20 ml), dried ($MgSO_4$) and evaporated to dryness to obtain a buff gum (170 mg). This gum was separated into 3 components by PLC (alumina, Merck) with 3 elutions using 40% chloroform in petrol (60-80°). Fraction A,(R_f 0.75, alumina,

chloroform) (84 mg) was dissolved in cyclohexane, treated with gaseous hydrogen chloride, 'degassed' with nitrogen, filtered, dried, and crystallized from water to afford 5-ethoxy-8,9-dimethoxy-2,3-methylenedioxyberbine hydrochloride (412) (61 mg., 32%) as a buff solid, m.p. 180-182°, $\nu_{max.}$(cm.$^{-1}$) ($CHBr_3$), nothing in range 3000-4000; NMR ($CDCl_3$) 1.21 (3H, t, J = 7 Hz; $-OCH_2\underline{CH_3}$); 2.5-4.0 (6H, m; $\underline{CH_2}$ at C-6, $\underline{CH_2}$ at C-8, $\underline{CH_2}$ at C-13); 3.64 (2H, q, J = 7 Hz; $-O\underline{CH_2}CH_3$); 4.1-4.4 (2H, m; C_5-$\underline{H}$ and C_{13}-$\underline{H}$); 5.92 (2H, s; $-O\underline{CH_2}O-$); 6.6-7.0 (4H, m; aromatics) (Found: C, 59.9; H, 6.2. $C_{22}H_{25}NO_5.HCl.H_2O$ requires C, 60.3; H, 6.4%).

Fractions B (R_f 0.33) and C (R_f 0.19), mutually contaminated (by TLC) were apparently samples of tetrahydroberberastine. IR spectra ($CHBr_3$) were identical except for B, 3250 cm.$^{-1}$ (broad, weak) and 3560 (m, sharp); for C, 3250 (broad, strong) and 3560 (weak, sharp).

Berberastine Iodide (413).

A boiling solution of tetrahydroberberastine hydrochloride (408) (100 mg., 0.255 mmol) and potassium acetate (300 mg., 3 mmol) in hot ethanol (3 ml) was treated with a solution of iodine (180 mg., 0.71 mmol) in ethanol by dropwise addition over 10 minutes, with immediate precipitation of a yellow solid. After boiling for a further 10 minutes the mixture was cooled, filtered, and the residue was washed with ethanol (2 x 1 ml), water (2 ml) and dried to obtain berberastine iodide (413) (97 mg., 80%) as a yellow solid, m.p. $\nless$ 300°, $\lambda_{max.}$(nm) (log ε) (H_2O) 228 (4.61),

265 (4.41), 345 (4.37), 4.26 (3.71), $\lambda_{min.}$ 211 (4.33), 251 (4.28), 304 (3.84), 376 (3.46), $\lambda_{inflex.}$ 273 (3.36) [lit.[5] $\lambda_{max.}$ (log ε) (H_2O) 228 (4.63), 265 (4.41), 344 (4.35), 424 (3.77), $\lambda_{min.}$ 212, 250, 302.5, 377]; $\nu_{max.}$ (KBr) 3240 (strong, OH), 1660-1620 (C=N) [spectrum of synthetic (413) very similar to that published for (413)]; NMR (100 MHz) (DMSO-d^6); 4.08 (3H, s; C_9-O$\underline{CH_3}$); 4.12 (3H, s; C_{10}-O$\underline{CH_3}$); 4.7-5.3 (3H, m; C_5-$\underline{H}$ and $\underline{CH_2}$ at C-6); 5.95-6.05 (1H, m, removed on deuteration; -$\underline{OH}$); 6.20 (2H, s; -O$\underline{CH_2}$O-); 7.16 (1H, s; C_4-H); 7.83 (1H, s; C_1-H); 8.02 (1H, d, J = 9 Hz; C_{11}-$\underline{H}$); 8.24 (1H, d, J = 9 Hz; C_{12}-$\underline{H}$); 9.01 (1H, s; C_8-$\underline{H}$); 9.98 (1H, s; C_{13}-$\underline{H}$) (Found: C, 50.4; H, 3.7; N, 2.8. $C_{20}H_{18}INO_5$ requires C, 50.1; H, 3.8; N, 2.9%).

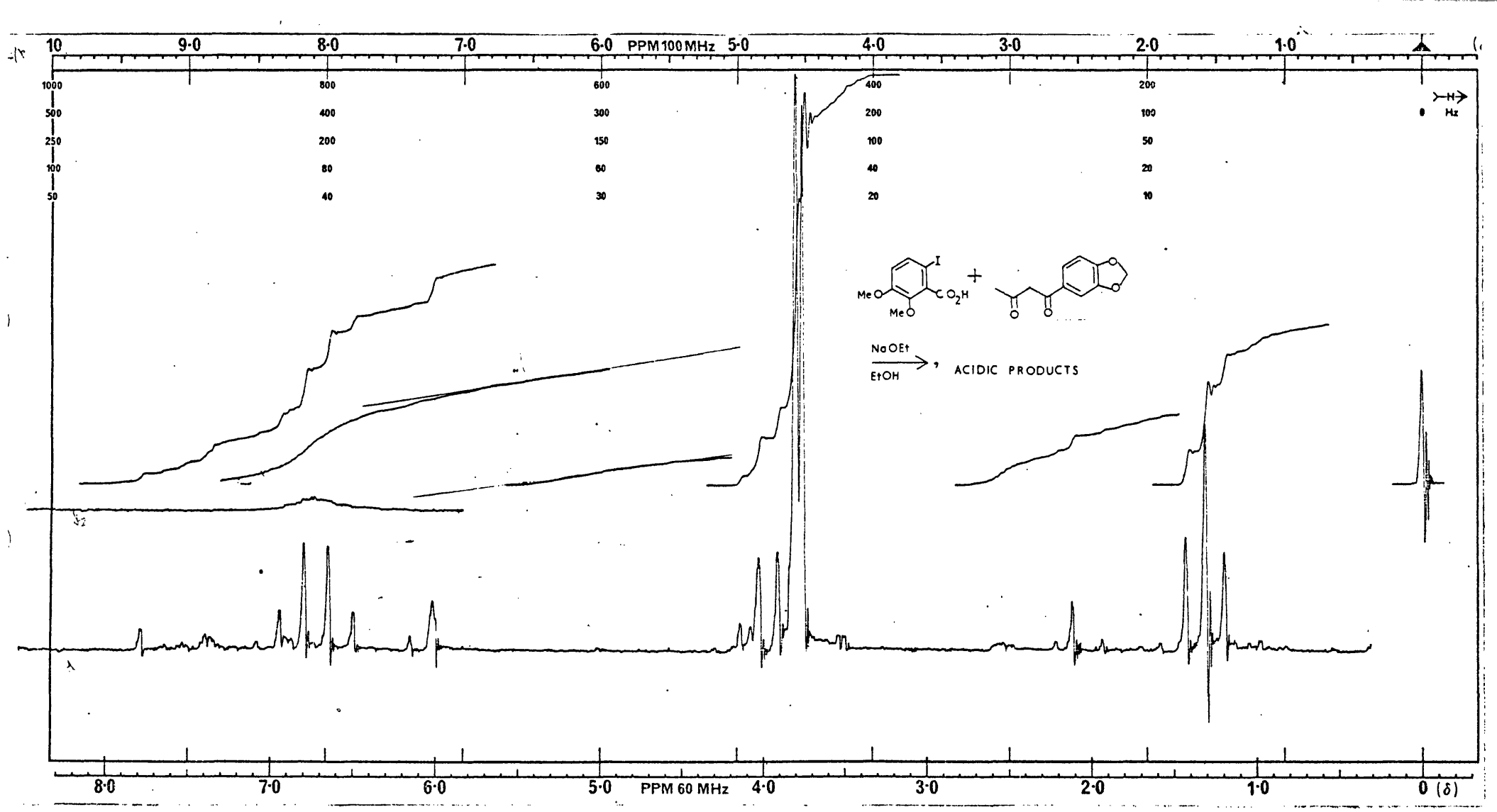
<u>10,11-Dimethoxy-5-hydroxy-2,3-methylenedioxyberbine hydrochloride (407)</u>.

N-(2,2-Dimethoxyethyl)-6,7-dimethoxy-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (406; R=H, R^1=OMe) (319 mg., 0.68 mmol) was added to 6N hydrochloric acid (8 ml) and the suspension was stirred at 21° for 18 hours. The mixture was filtered and the residue was washed with water (3 x 2 ml) and dried to afford 10,11-dimethoxy-5-hydroxy-2,3-methylenedioxyberbine hydrochloride (407) (149 mg., 56%) as a pale buff solid, m.p. 191-193° (lit.[29] m.p. 188-190°) mixed m.p. 190-192° (Found: C, 60.4; H, 6.3; N, 3.4. Calcd. for $C_{20}H_{21}NO_5$.HCl.H_2O. C, 60.3; H, 6.4; N, 3.3%).

Methyl [7,8-dimethoxy-2-methyl-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinol-4-yl] acetate hydrochloride (422; R=Me).

Glyoxylic acid monohydrate (3.80 g., 41 mmol) was added to a solution of N-methyl-N-(2,3-dimethoxybenzyl)-α-amino-(3,4-methylenedioxyphenylacetaldehyde dimethyl acetal (364) (1.80 g., 4.65 mmol) in 36% hydrochloric acid (50 ml) and the resultant solution was heated on a steam bath for 1.8 hours, then evaporated to near dryness. The residue was dissolved in isopropanol (50 ml) and the solution was evaporated to near dryness. This was repeated with further isopropanol (50 ml) and the residue was shaken with 2N ammonia solution and carbon tetrachloride (50 ml). The aqueous phase was extracted with further carbon tetrachloride (2 x 50 ml), then the aqueous solution was evaporated to near dryness. The residue was dissolved in ethanol (100 ml) and sodium borohydride (4.0 g.) was added to the stirred solution. After 18 hours at 21°, the mixture was evaporated to near dryness and the residue was shaken with water (100 ml) and 25% chloroform in carbon tetrachloride (20 ml). The mixture was filtered and the aqueous phase was extracted with a further portion of 25% chloroform in carbon tetrachloride (20 ml). The aqueous solution was evaporated to near dryness with the aid of isopropanol (3 x 50 ml) and the residue was dissolved in 2N hydrochloric acid (20 ml) and chloroform (20 ml). The aqueous phase was extracted with chloroform (8 x 20 ml) and the combined chloroform extracts were dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in ethanol (20 ml) and treated with diazomethane (ca. 3 g.) in ether (150 ml). After 20 minutes, nitrogen was bubbled through the solution for 1 hour, then the solution was decanted from a small amount of oil,

washed with saturated sodium carbonate solution, and extracted with 2N sulphuric acid (3 x 40 ml). The combined acid extracts were basified with aqueous ammonia (d 0.88) and extracted with ether (80 ml, 3 x 40 ml). The combined ethereal extracts were washed with brine (2 x 40 ml), dried (Na_2SO_4), and evaporated to dryness to afford (422; R=Me) (0.388 g., 19%) as a yellow gum. The gum was dissolved in cyclohexane and hydrogen chloride gas was passed, then the mixture was purged with nitrogen, filtered, and the pale grey solid was washed with petrol (40-60°) and dried to give <u>methyl 7,8-dimethoxy-2-methyl-3-(3,4-methylene-dioxyphenyl)-1,2,3,4-tetrahydroisoquinol-4-yl acetate hydrochloride (422; R=Me)</u>, (0.415 g., 19%), m.p. 126°, $\lambda_{max.}$ (nm) (ε) (EtOH) 206 (58,700), 233 (12,100), 287 (3,550), $\lambda_{min.}$ 229 (11,800), 262 (2,130); $\nu_{max.}$ ($cm.^{-1}$) (free base) ($CHBr_3$) 2850 (OMe) 2790 (w), 1730 (CO_2Me) 935 (OCH_2O); NMR ($CDCl_3$) (free base) 2.23 (15% of 3H, s; $-\overset{|}{N}-\underline{CH_3}$); 2.32 (85% of 3H, s; $-\overset{|}{N}-\underline{CH_3}$); 2.56 (2H, broad, d, $J \simeq 7$ Hz; $-\underline{CH_2}CO_2CH_3$); 3.55 (3H, s; $-CO_2\underline{CH_3}$); 3.84 (6H, s, 2 x Ar-$O\underline{CH_3}$); 3.4-4.2 (4H, m; $C_3-\underline{H}$, $C_4-\underline{H}$, $Ar\underline{CH_2}-\overset{|}{N}-$); 5.88 (2H, s; $-O\underline{CH_2}O-$); 6.5-7.2 (5H, m; aromatics) (Found: C, 60.5; H, 6.0; N, 3.4. $C_{22}H_{25}NO_6.HCl$ requires C, 60.6; H, 6.0; N, 3.2%).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Hz
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100
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800
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80
40
600
300
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60
30
400
200
100
40
20
200
100
50
20
10
I
MeO
MeO
CO2H
+
NaOEt
EtOH
ACIDIC PRODUCTS
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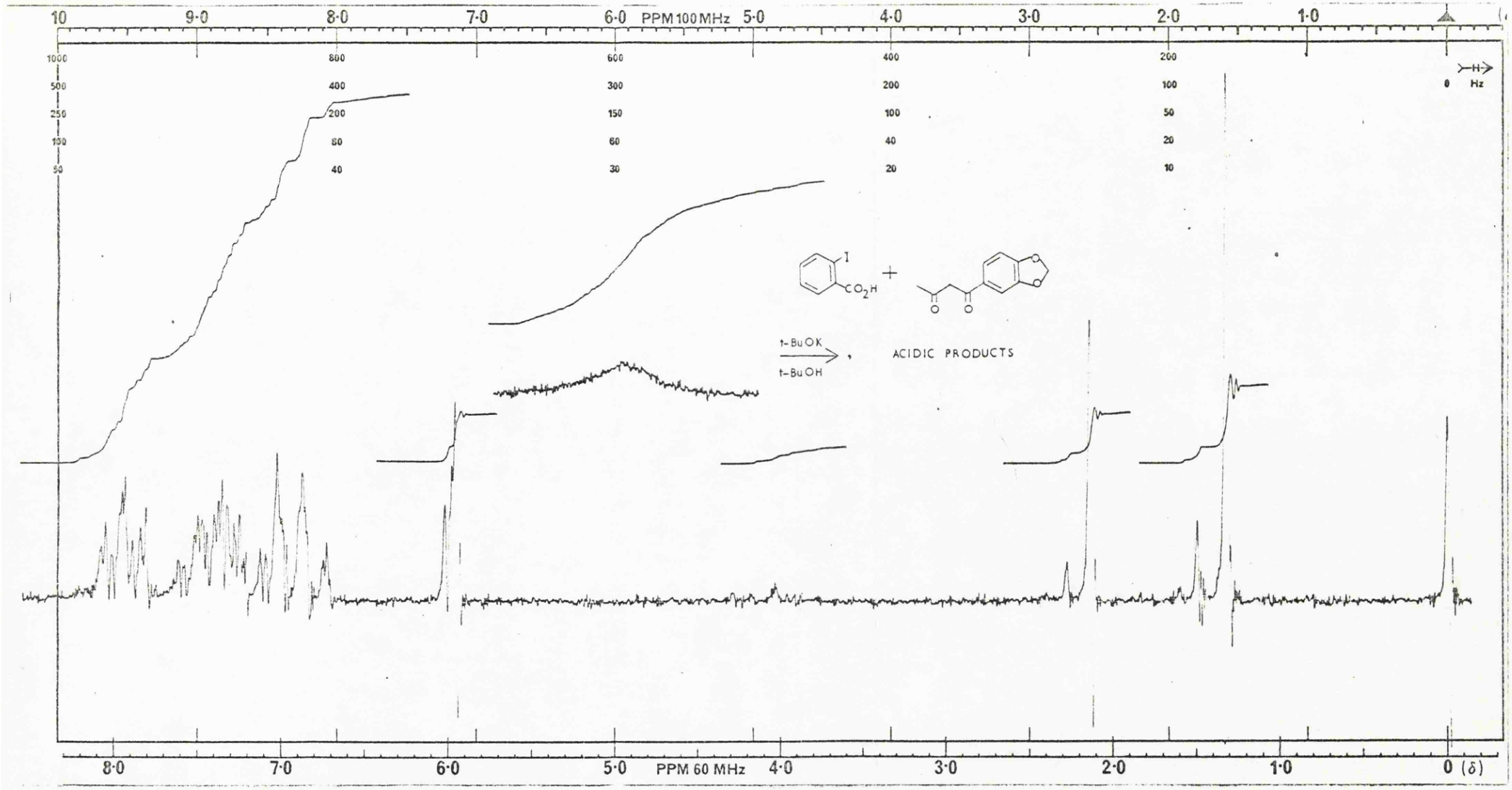
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)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2·0
1·0
Hz
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CO_2H
+
t-BuOK
t-BuOH
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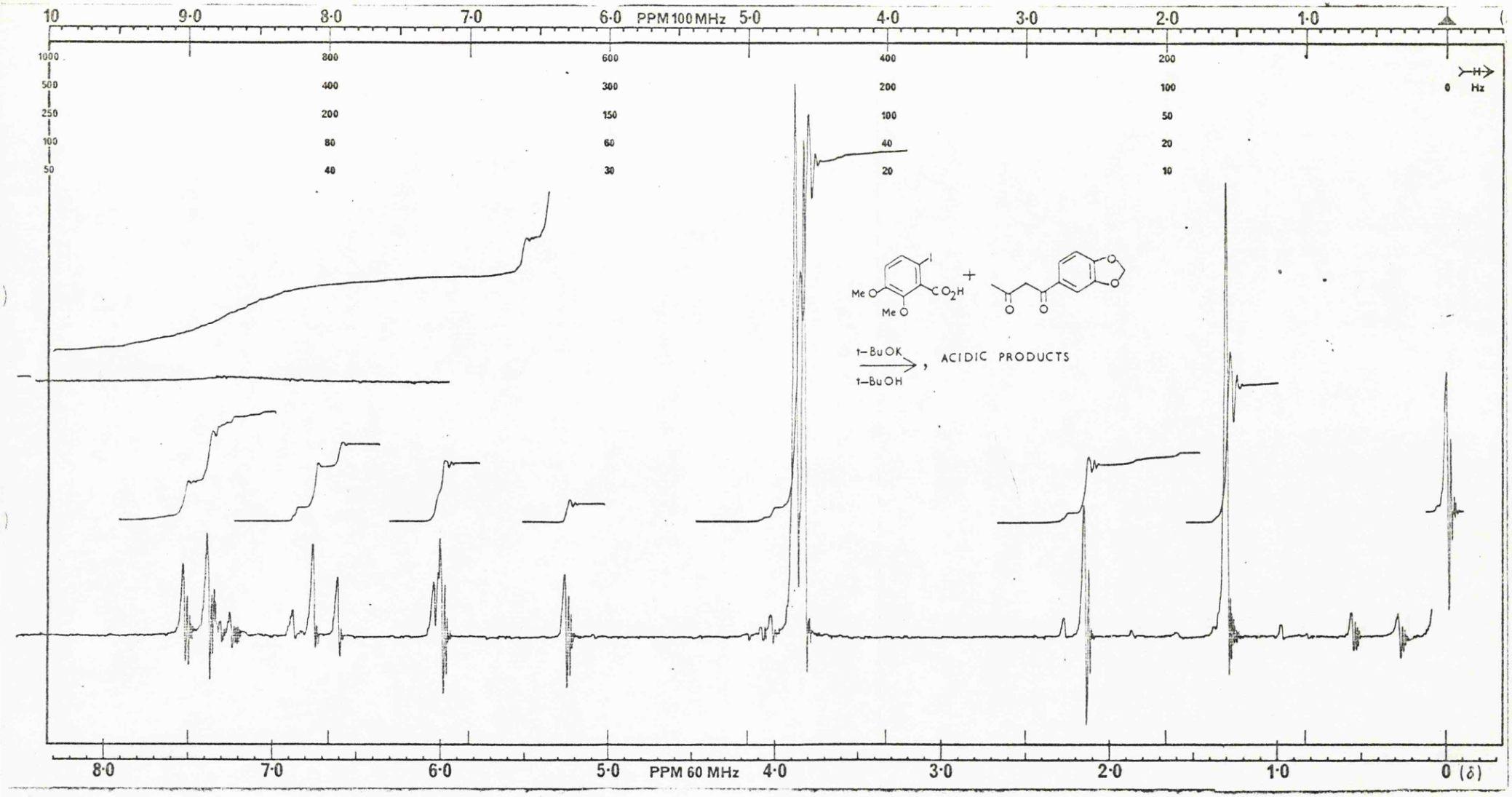
4·0
3·0
2·0
1·0
0 (δ)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50 40 30 20 10
0 Hz
Me O
Me O
I
CO2H
t-BuOK
t-BuOH
ACIDIC PRODUCTS
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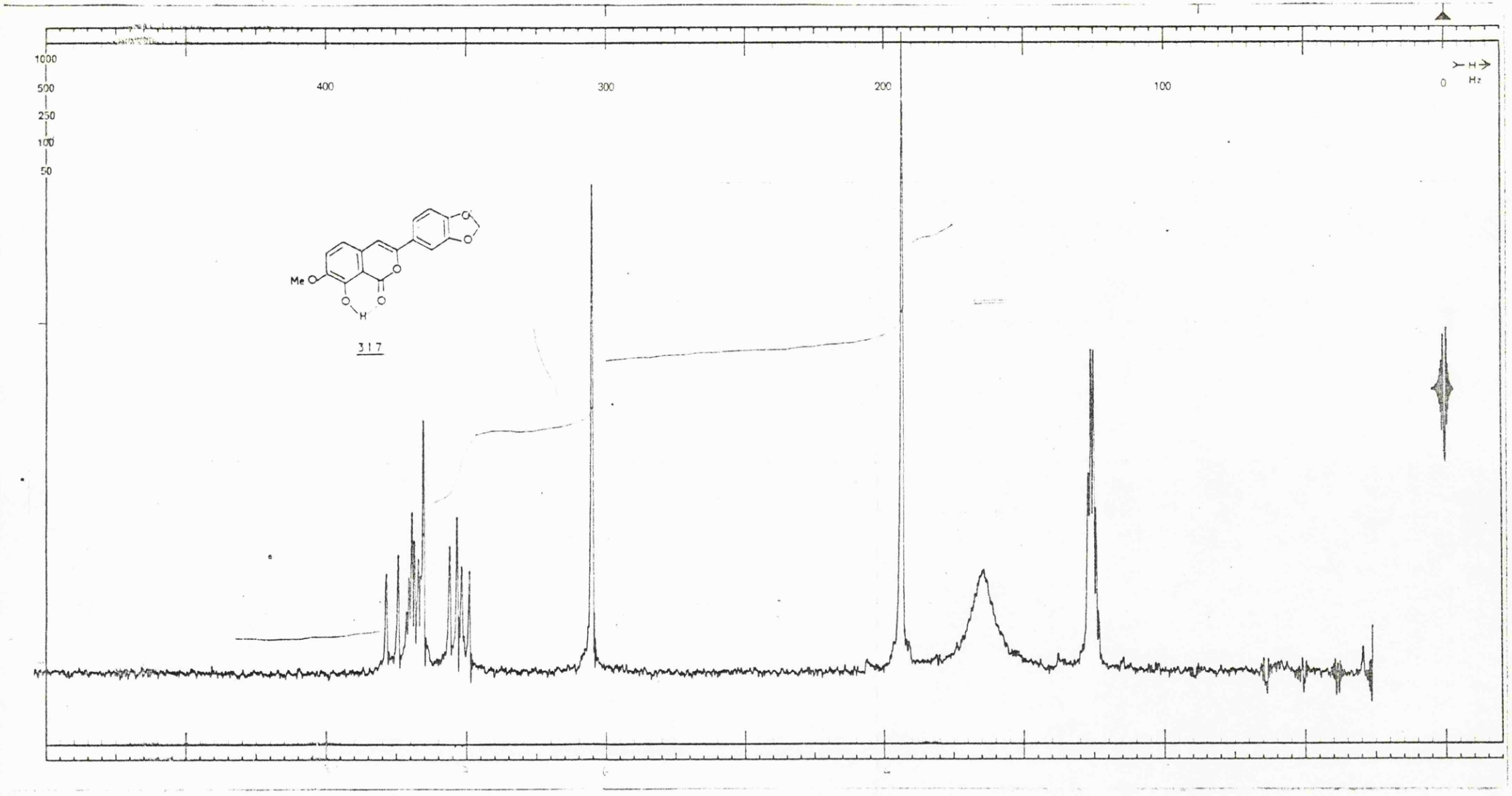

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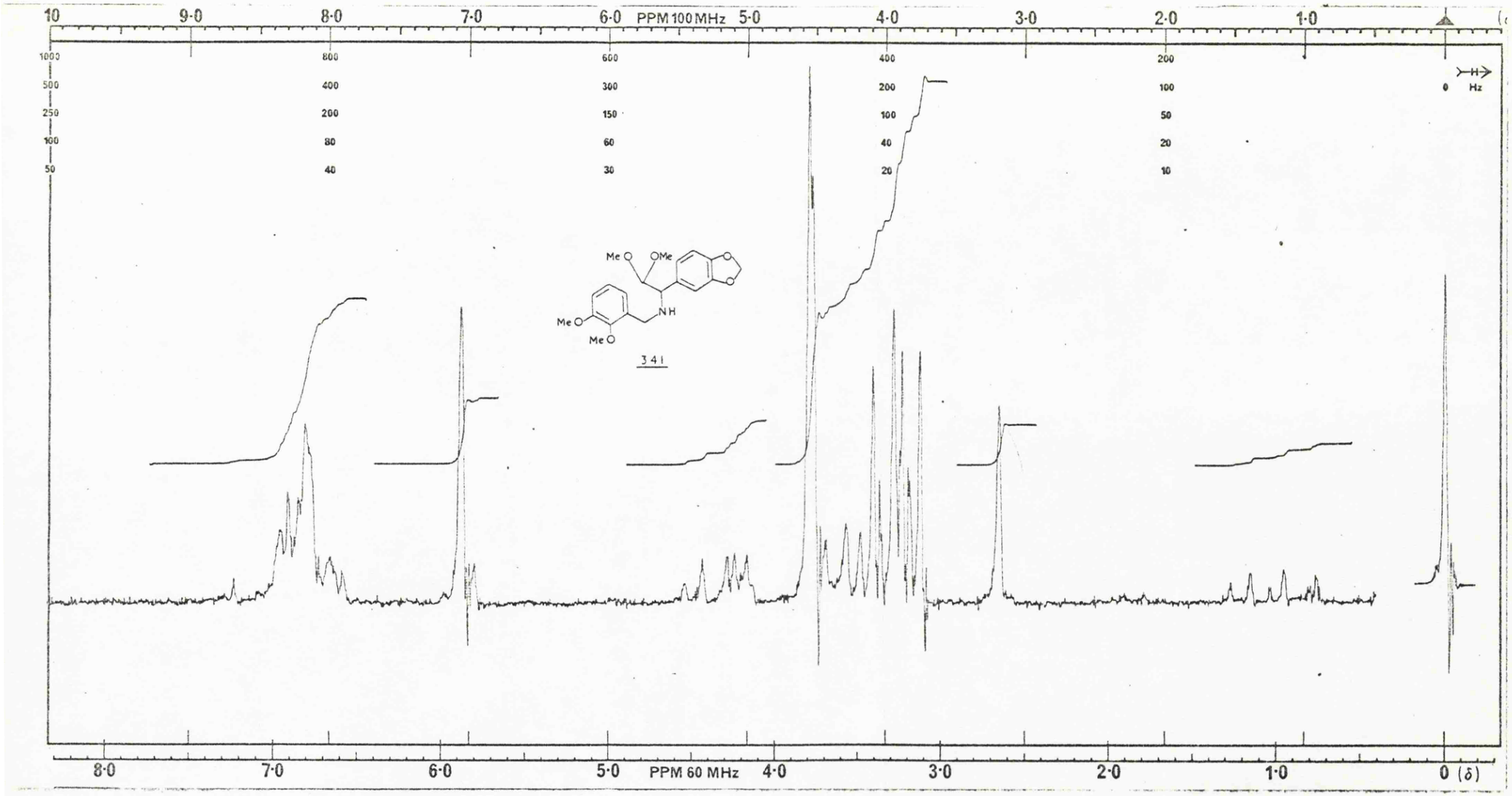
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250
100
50
800
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200
80
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30
400
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100
40
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200
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OMe
NH
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3·0
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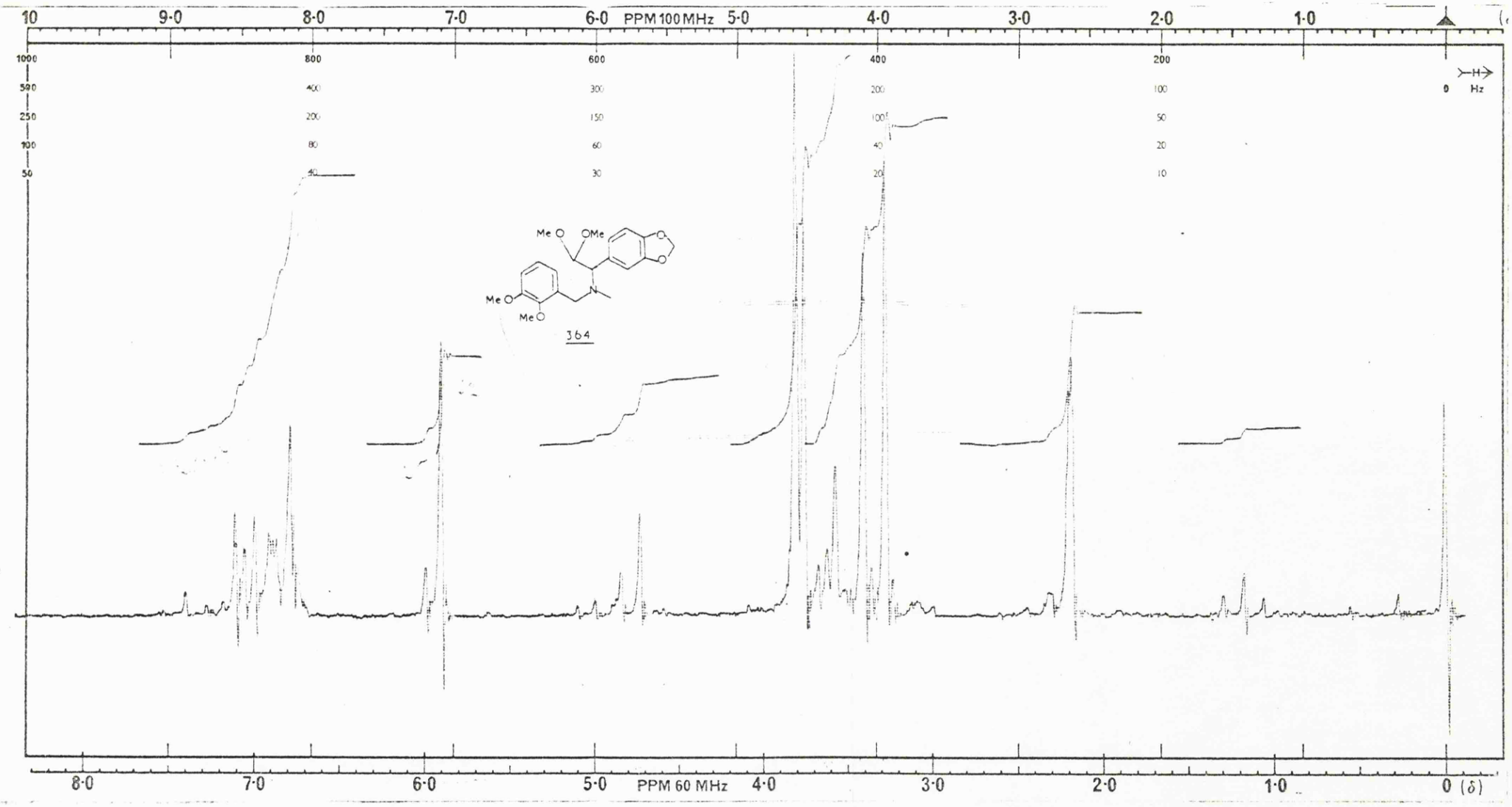
1·0
0 (δ)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OMe
Me O
Me O
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5·0
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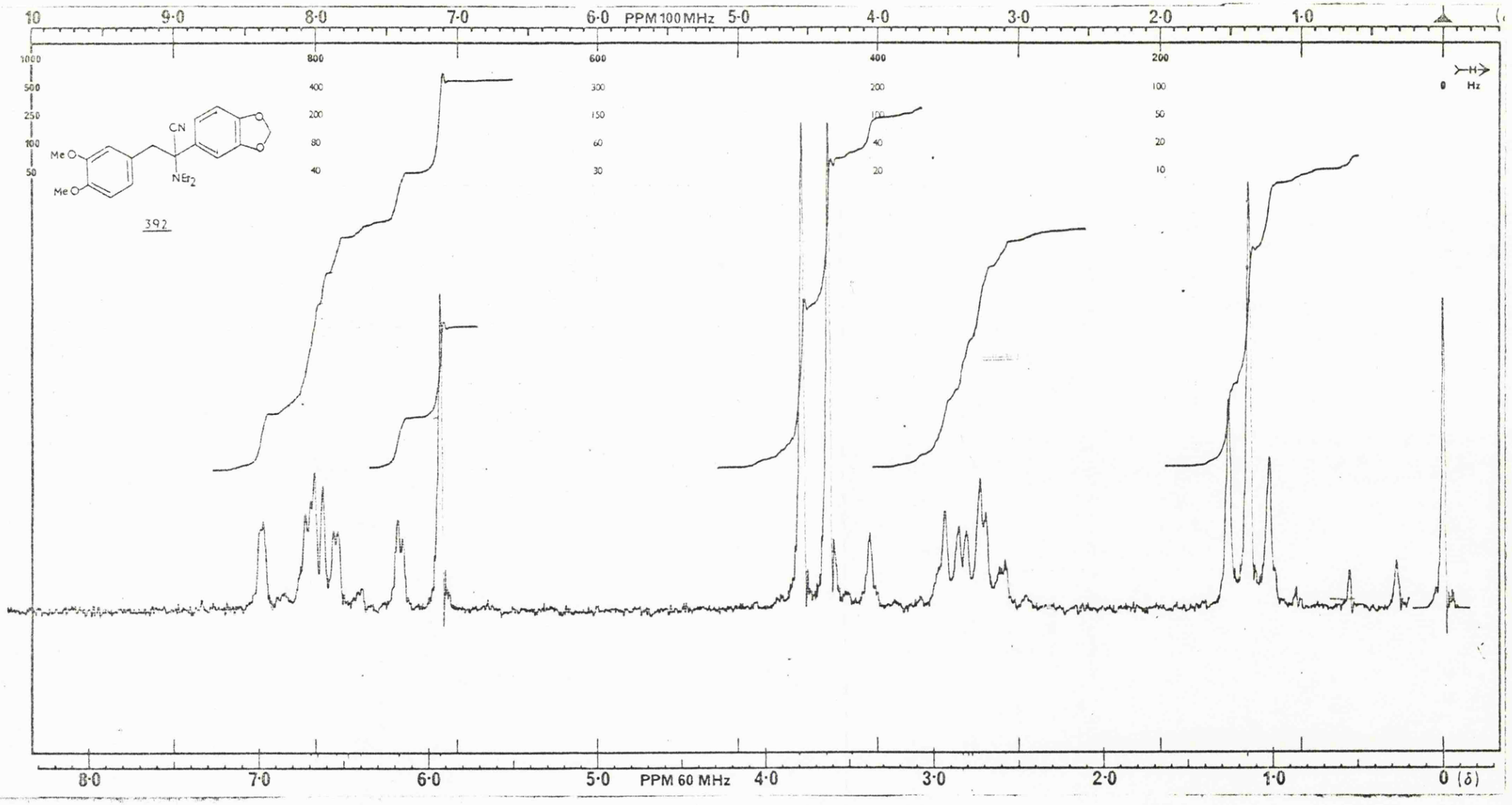
2·0
1·0
0 (δ)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0
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CN
Me O
Me O
NEt2
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7·0
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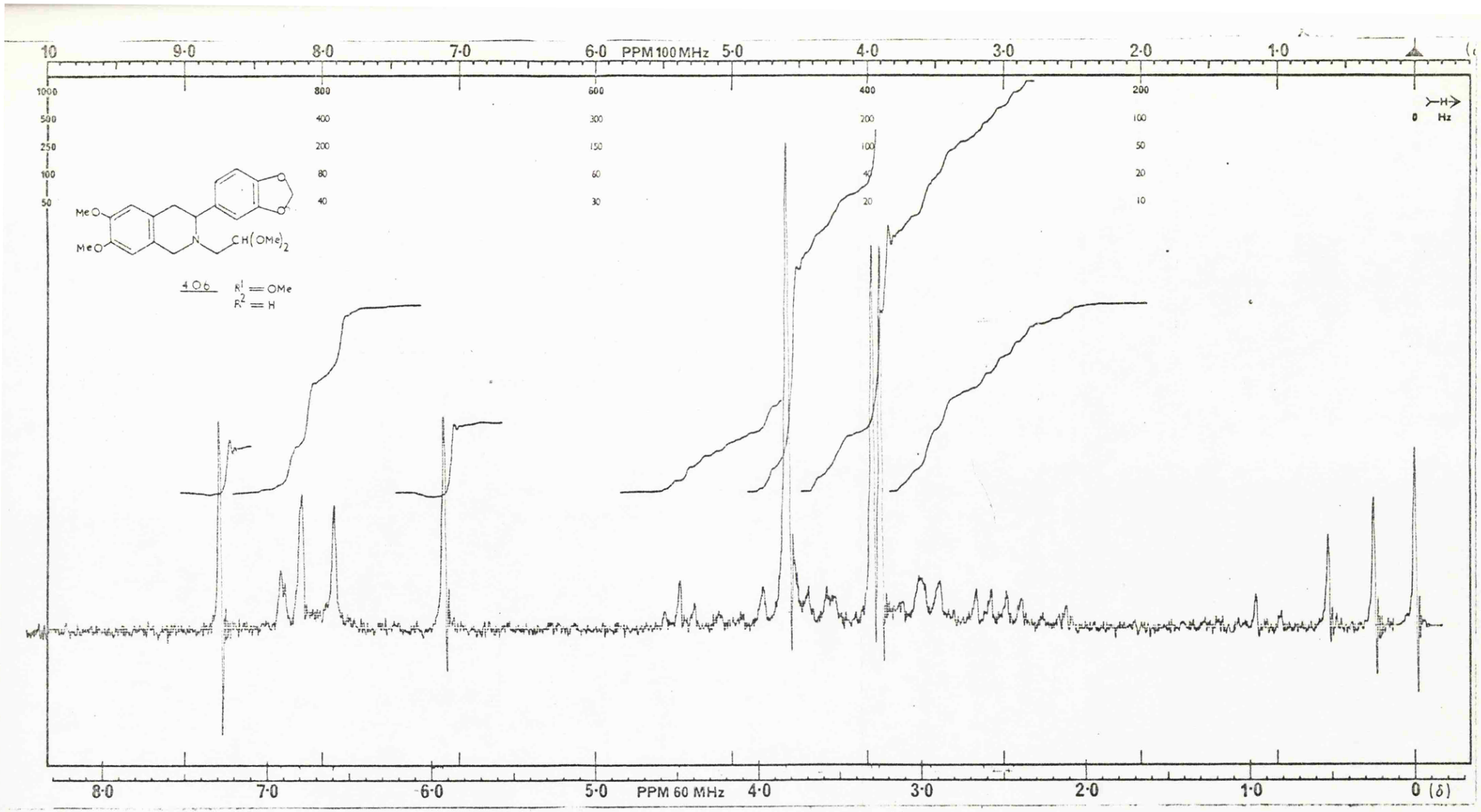
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)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3·0
2·0
1·0
0 Hz
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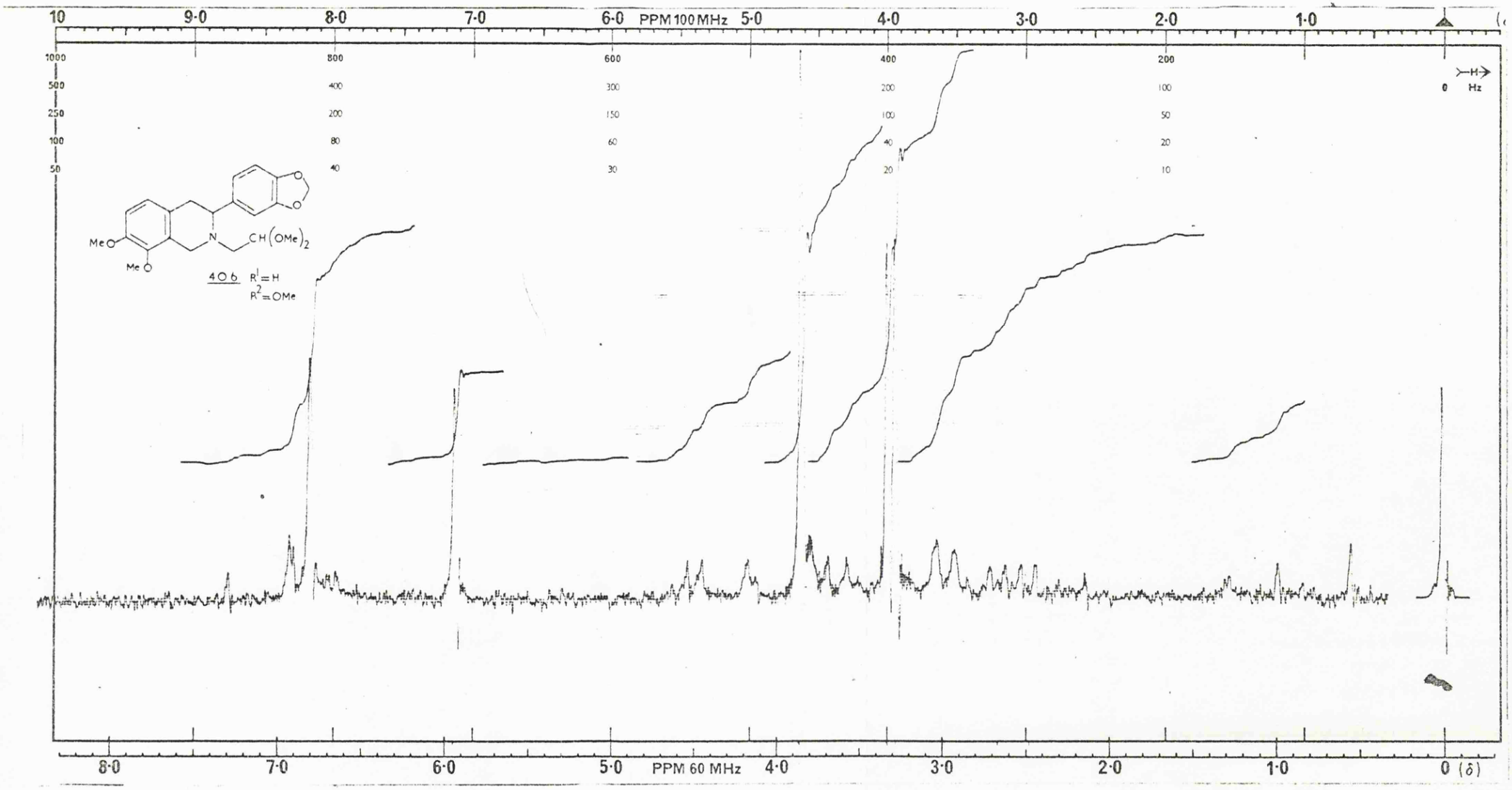
MeO
N
CH(OMe)2
4.06
R1 = OMe
R2 = H
8·0
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)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2·0
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0 Hz
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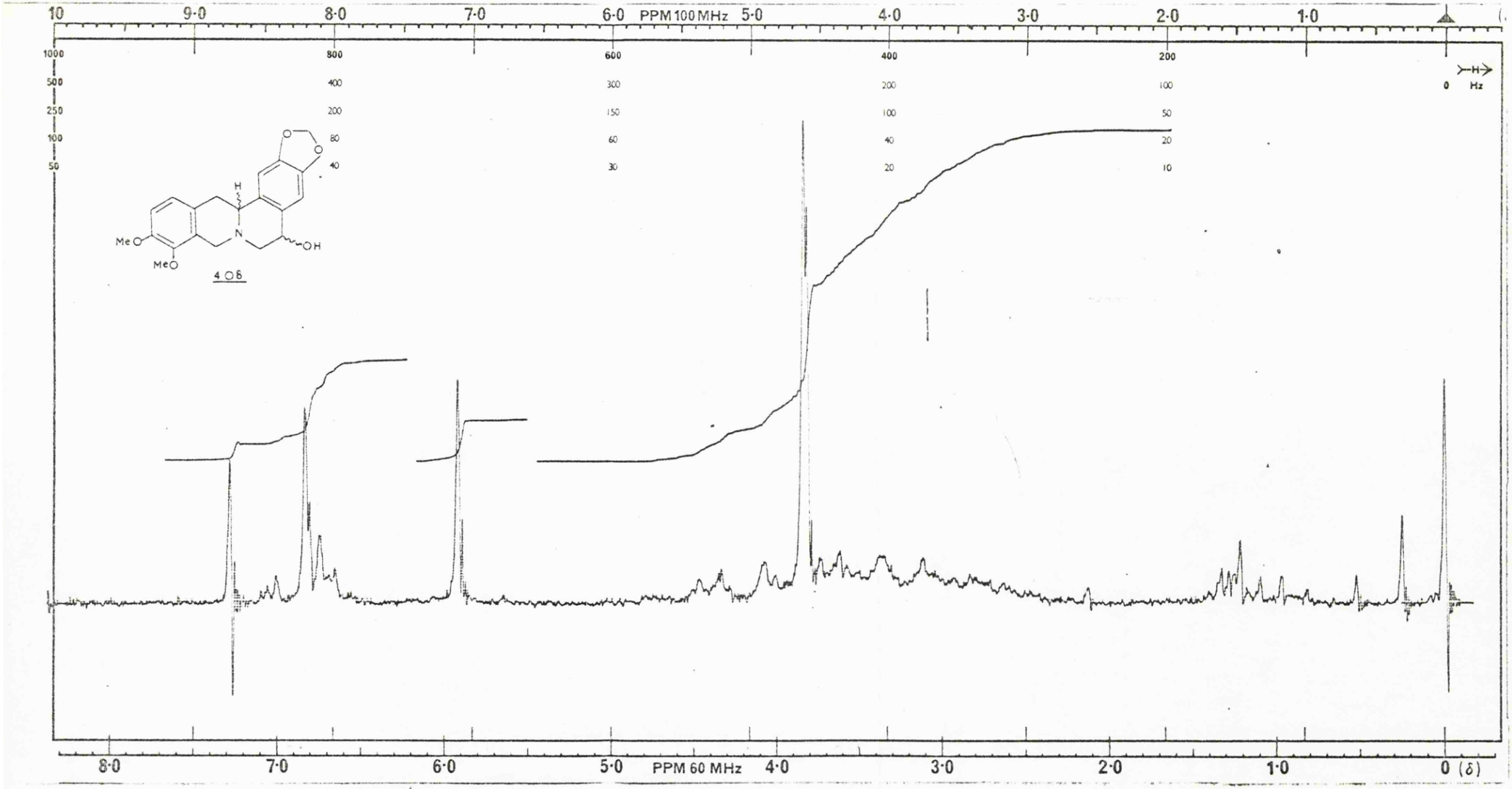
N
CH(OMe)2
406 R1=H
R2=OMe
8·0
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)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8·0
7·0
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4·0
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2·0
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400
200
80
40
600
300
150
60
30
400
200
100
40
20
200
100
50
20
10
H
0 Hz
Me O
MeO
N
H
OH
O
O
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7·0
6·0
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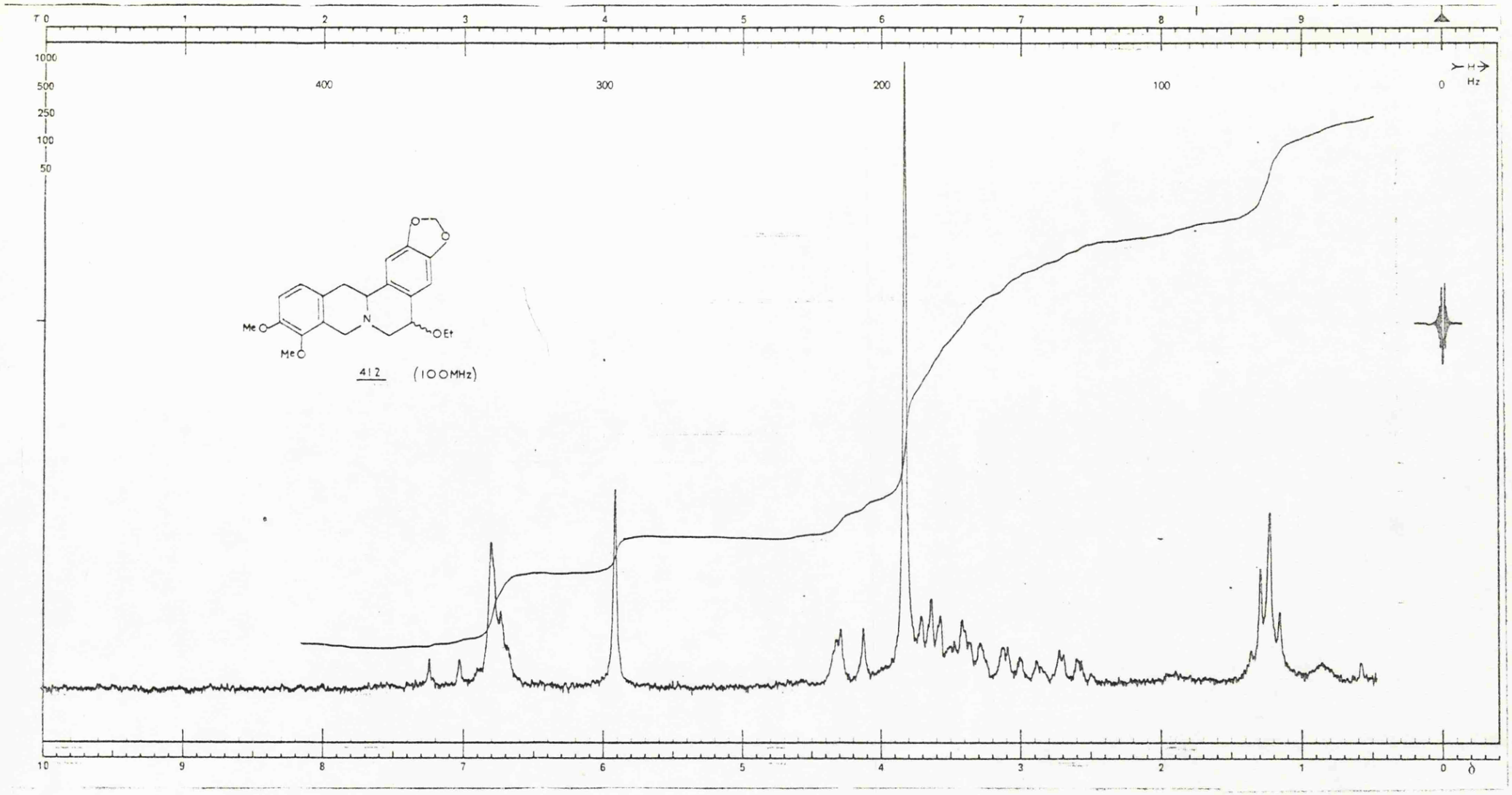
3·0
2·0
1·0
0 (δ)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2
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7
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9
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500
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100
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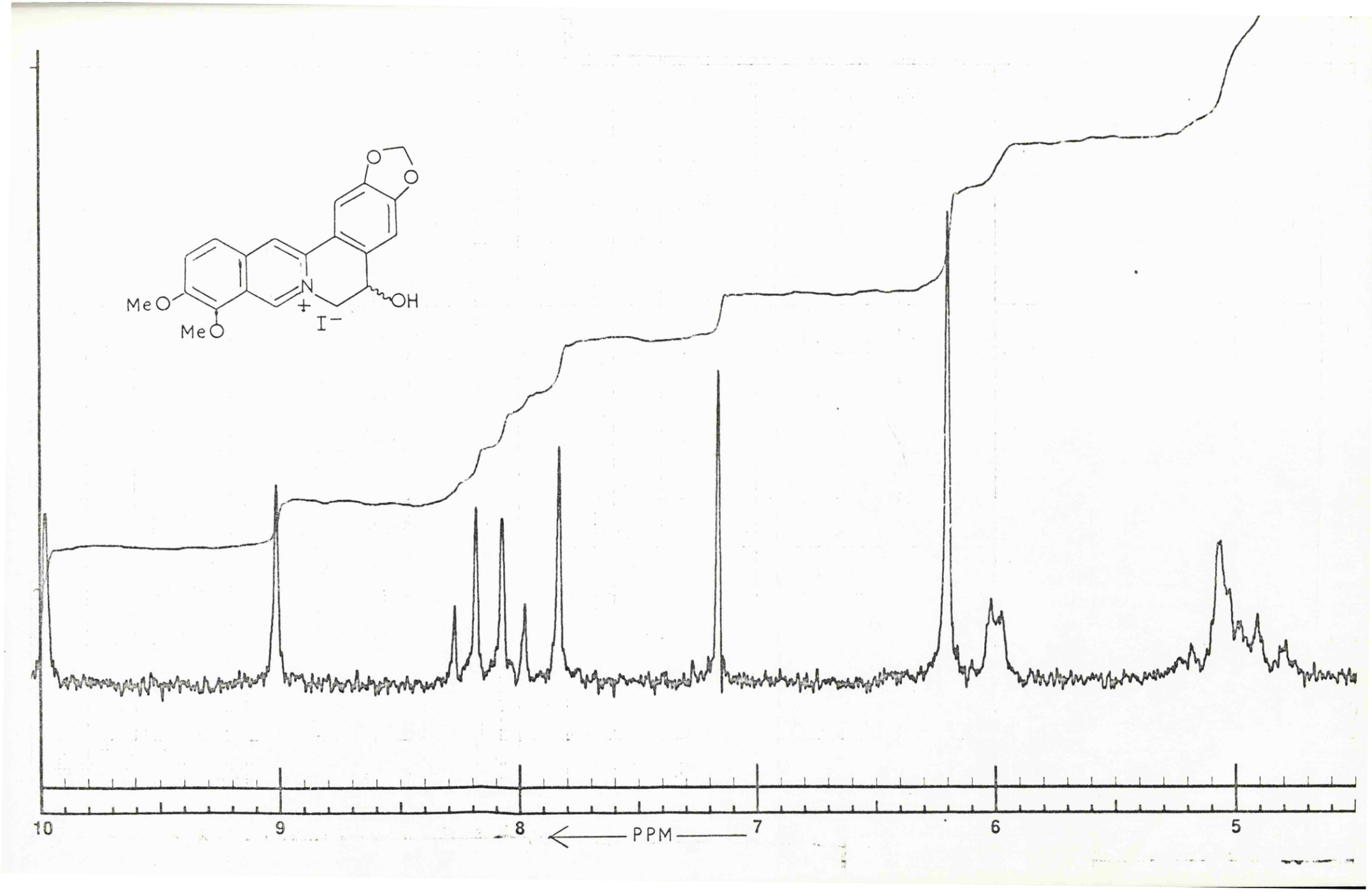
400
300
200
100
0
Hz
Me O
Me O
N
OEt
412 (100MHz)
10
9
8
7
6
5
4
3
2
1
0
δ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+
I⁻
OH
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PPM
7
6
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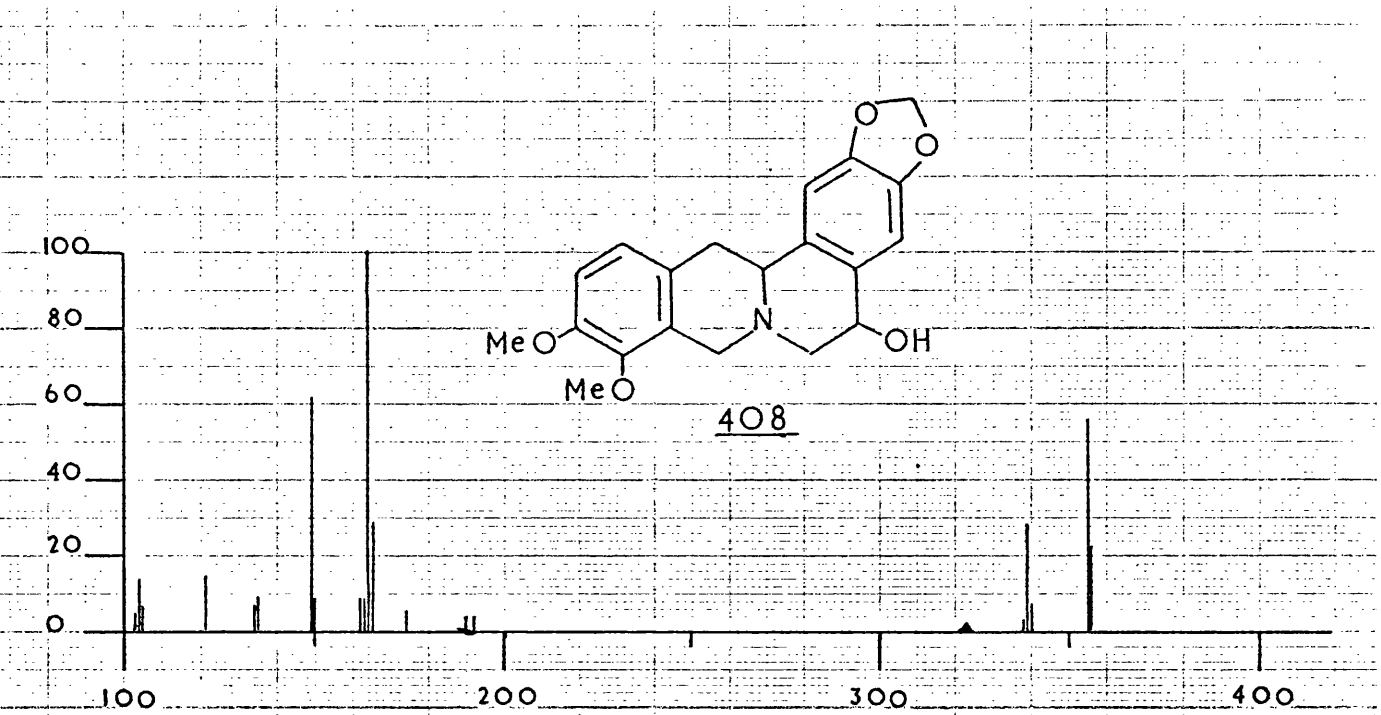
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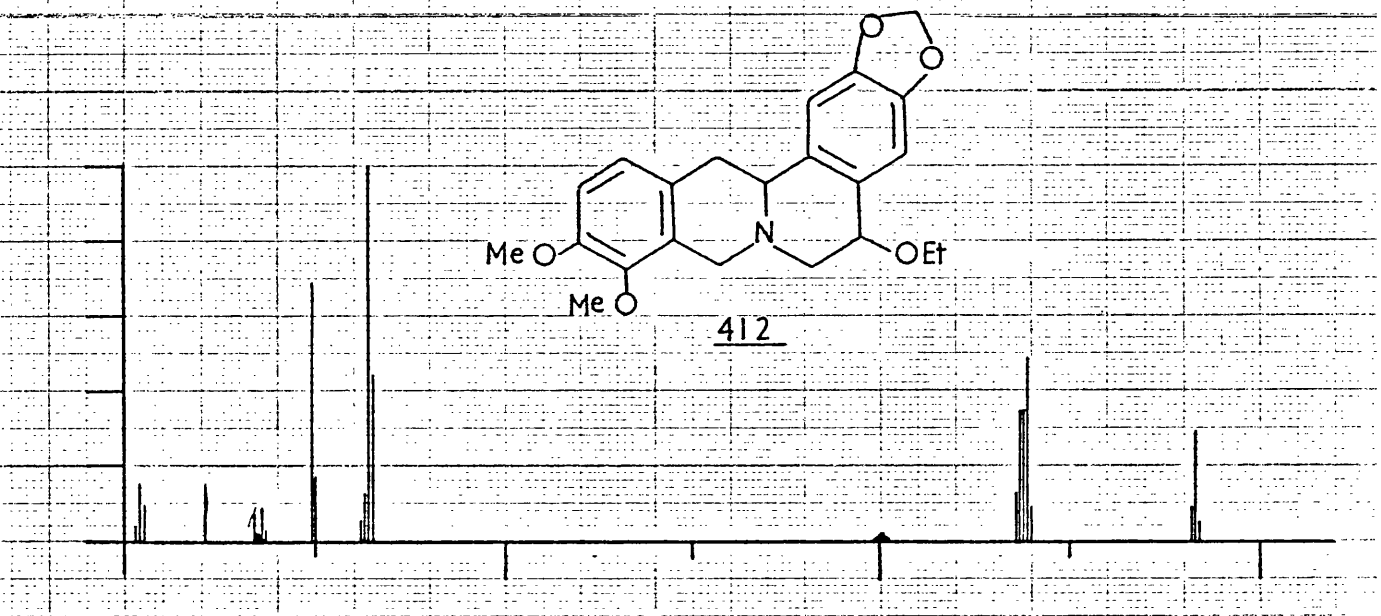
O
O

408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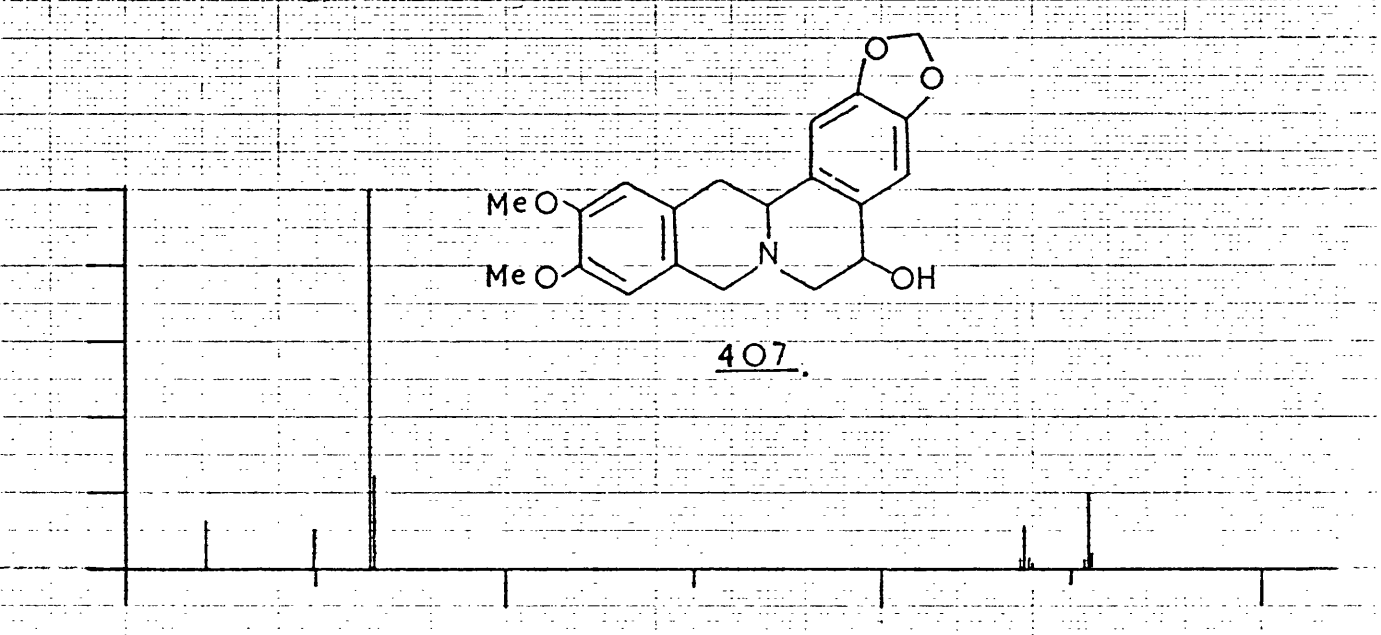
O

412


Me O
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OH
N
O
O

407

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